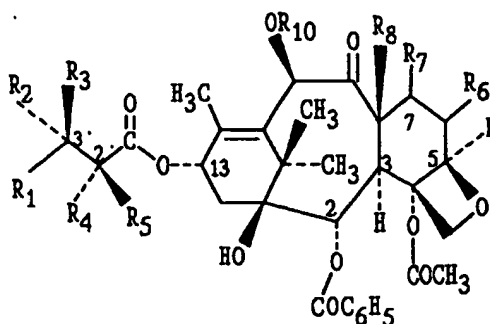


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 305/14, 413/12, 263/04		A1	(11) International Publication Number: WO 94/13655
			(43) International Publication Date: 23 June 1994 (23.06.94)
(21) International Application Number: PCT/US93/11827		(72) Inventors; and	
(22) International Filing Date: 13 December 1993 (13.12.93)		(75) Inventors/Applicants (for US only): HESTER, Jackson, B., Jr. [US/US]; 9219 East ML Avenue, Galesburg, MI 49053 (US). JOHNSON, Roy, A. [US/US]; 2122 Frederick Avenue, Kalamazoo, MI 49008 (US). KELLY, Robert, C. [US/US]; 936 East Gull Lake Drive, Augusta, MI 49012 (US). MIDY, Eldon, G. [US/US]; 3103 Morgan Street, Kalamazoo, MI 49009 (US). SKULNICK, Harvey, I. [US/US]; 1745 Old Deer Run, Kalamazoo, MI 49009 (US).	
(30) Priority Data:		(74) Agent: JAMESON, William, G.; Corporate Intellectual Property Law, The Upjohn Company, 301 Henrietta Street, Kalamazoo, MI 49001 (US).	
07/990,579 15 December 1992 (15.12.92) US			
08/013,826 2 February 1993 (02.02.93) US			
08/076,337 11 June 1993 (11.06.93) US			
08/122,974 17 September 1993 (17.09.93) US			
(60) Parent Applications or Grants		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(63) Related by Continuation		Published	
US 07/990,579 (CIP)		With international search report.	
Filed on 15 December 1992 (15.12.92)			
US 08/013,826 (CIP)			
Filed on 2 February 1993 (02.02.93)			
US 08/076,337 (CIP)			
Filed on 11 June 1993 (11.06.93)			
US 08/122,974 (CIP)			
Filed on 17 September 1993 (17.09.93)			
(71) Applicant (for all designated States except US): THE UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).			

(54) Title: 7-HALO- AND 7 β ,8 β -METHANO-TAXOLS, ANTINEOPLASTIC USE AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract

This invention provides 7-deoxy-taxol analogs of formula (I). The compounds of formula (I) (including formulae II and III) are useful for the same cancers for which taxol has been shown active, including human ovarian cancer, breast cancer, and malignant melanoma as well as lung cancer, gastric cancer, colon cancer, head and neck cancer, and leukemia.

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

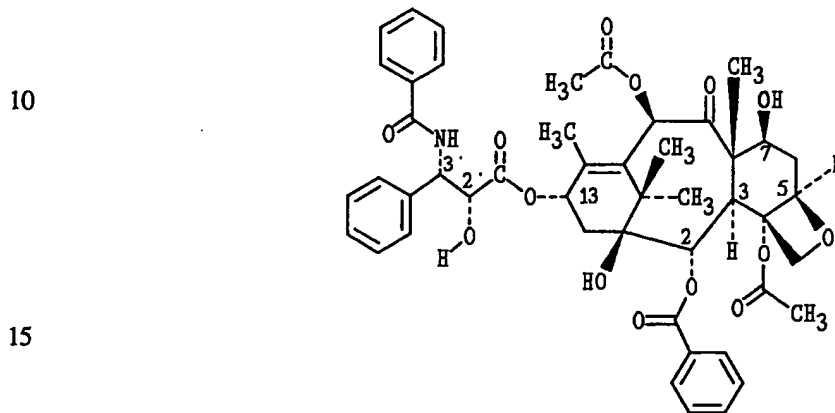
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

7-HALO- AND 7 β ,8 β -METHANO-TAXOLS,
ANTINEOPLASTIC USE AND PHARMACEUTICAL
COMPOSITIONS CONTAINING THEM

BACKGROUND OF THE INVENTION

5 Taxol is a member of the taxane family of diterpenes, having the structure shown below:



The numbering system shown for taxol is that recommended by IUPAC (IUPAC, Commission
20 on the Nomenclature of Organic Chemistry, 1978).

The chemistry of the potent anticancer diterpenoid taxol and analogs thereof is reviewed,
with an emphasis on isolation and analysis, structural modifications, partial synthesis, and
structure-activity relationships by David G.I. Kingston, The Chemistry of Taxol, Pharmac. Ther.,
Vol 52, pp 1-34, 1991.

25 The clinical pharmacology of taxol is reviewed by Eric K. Rowinsky and Ross C.
Donehower, The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer
Chemotherapeutics, Pharmac. Ther., Vol 52, pp 35-84, 1991. Clinical and preclinical studies
with taxol are reviewed by William J. Slichenmyer and Daniel D. Von Hoff, Taxol: A New and
Effective Anti-cancer Drug, Anti-Cancer Drugs, Vol. 2, pp 519-530, 1991.

30 Taxol and analogs thereof are the subject of various patents including, for example, U.S.
Patent Nos. 4,814,470; 4,857,653; 4,942,184; 4,924,011; 4,924,012; 4,960,790; 5,015,744;
5,157,049; 5,059,699; 5,136,060; 4,876,399; 5,227,400 as well as PCT Publication No.
WO 92/09589, European Patent Application 90305845.1 (Publication No. A2 0 400 971),
90312366.9 (Publication No. A1 0 428 376), 89400935.6 (Publication No. A1 0 366 841) and
35 90402333.0 (Publication No. 0 414 610 A1), 87401669.4 (A1 0 253 739), 92308608.6 (A1 0
534 708), 92308609.4 (A1 534 709) and PCT Publication Nos. WO 91/17977, WO 91/17976,

WO 91/13066, WO 91/13053.

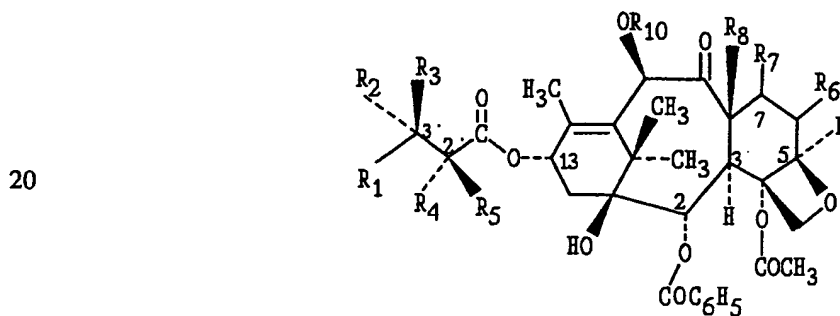
Various processes for the preparation of taxol (and intermediates and analogs thereof) are described in Tetrahedron Letters, 1992, 33, 5185; J. Org. Chem., 1991, 56, 1681 and J. Org. Chem., 1991, 56, 5114.

5 Chen et al., Serendipitous Synthesis of a Cyclopropane-Containing Taxol Analog via Anchimeric Participation of an Unactivated Angular Methyl Group, Advance ACS Abstracts, Vol 1, No. 2., July 15, 1993 reported the treatment of a 7-*epi* taxol derivative with DAST in dichloromethane led to an unexpected reaction involving participation of the C-19 methyl group and clean formation of a cyclopropane ring. See also J. Org. Chem., 1993, 58, 4520 (August
10 13, 1993).

U.S. Patent 5,248,796 (granted 28 September 1993) relates to 10-desacetoxy-11,12-dihydrotaxol-10,12(18)-diene derivatives and the preparation of 10-desacetoxytaxol.

SUMMARY OF THE INVENTION

15 This invention provides 7-deoxy-taxol analogs of Formula I:



25

I

The compounds of Formula I are useful for the same cancers for which taxol has been shown active, including human ovarian cancer, breast cancer, and malignant melanoma as well as lung cancer, gastric cancer, colon cancer, head and neck cancer, and leukemia.

30

CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a
35 numerical subscript, for example, "Z₁" or "R_i" where "i" is an integer. These variable substituents are either monovalent or bivalent, that is, they represent a group attached to the

formula by one or two chemical bonds. For example, a group Z_1 would represent a bivalent variable if attached to the formula $\text{CH}_3\text{-C}(=\text{Z}_1)\text{H}$. Groups R_i and R_j would represent monovalent variable substituents if attached to the formula $\text{CH}_3\text{-CH}_2\text{-C}(\text{R}_i)(\text{R}_j)\text{-H}$. When chemical formulas are drawn in a linear fashion, such as those above, variable substituents contained in parentheses are bonded to the atom immediately to the left of the variable substituent enclosed in parenthesis. When two or more consecutive variable substituents are enclosed in parentheses, each of the consecutive variable substituents is bonded to the immediately preceding atom to the left which is not enclosed in parentheses. Thus, in the formula above, both R_i and R_j are bonded to the preceding carbon atom. Also, for any molecule with an established system of carbon atom numbering, such as taxol, these carbon atoms are designated as C_i , where "i" is the integer corresponding to the carbon atom number. For example, C_6 represents the 6 position or carbon atom number in the nucleus as traditionally designated by those skilled in the art.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus $\text{CH}_3\text{-O-CH}_2\text{-CH}(\text{R}_i)\text{-CH}_3$ represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., $\text{CH}_2=\text{C}(\text{R}_i)\text{-O-CH}_3$, and the symbol " \equiv " represents a triple bond, e.g., $\text{HC}\equiv\text{C-CH}(\text{R}_i)\text{-CH}_2\text{-CH}_3$. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)- , with the former being preferred for simplicity.

Chemical formulas of cyclic (ring) compounds or molecular fragments can be represented in a linear fashion. Thus, the compound 4-chloro-2-methylpyridine can be represented in linear fashion by $\text{N}^*=\text{C}(\text{CH}_3)\text{-CH=CCl-CH=C}^*\text{H}$ with the convention that the atoms marked with an asterisk (*) are bonded to each other resulting in the formation of a ring. Likewise, the cyclic molecular fragment, 4-(ethyl)-1-piperazinyl can be represented by $\text{-N}^*-(\text{CH}_2)_2\text{-N}(\text{C}_2\text{H}_5)\text{-CH}_2\text{-C}^*\text{H}_2$. Similarly, 2-furyl can be represented by $\text{-C}^*\text{-O-CH=CH-C}^*\text{H=}$ and 2-thienyl represented by $\text{-C}^*\text{-S-CH=CH-C}^*\text{H=}$.

A rigid cyclic (ring) structure for any compounds herein defines an orientation with respect to the plane of the ring for substituents attached to each carbon atom of the rigid cyclic compound. For saturated compounds which have two substituents attached to a carbon atom which is part of a cyclic system, $\text{-C}(\text{X}_1)(\text{X}_2)\text{-}$ the two substituents may be in either an axial or equatorial position relative to the ring and may change between axial/equatorial. However, the position of the two substituents relative to the ring and each other remains fixed. While either substituent at times may lie in the plane of the ring (equatorial) rather than above or below the plane (axial), one substituent is always above the other. In chemical structural formulas depicting such compounds, a substituent (X_1) which is "below" another substituent (X_2) will be identified as being in the alpha (α) configuration and is identified by a broken, dashed or dotted

line attachment to the carbon atom, i.e., by the symbol "- - -" or "...". The corresponding substituent attached "above" (X_2) the other (X_1) is identified as being in the beta (β) configuration and is indicated by an unbroken line attachment to the carbon atom.

When a variable substituent is bivalent, the valences may be taken together or separately or both in the definition of the variable. For example, a variable R_i attached to a carbon atom as $-C(=R_i)-$ might be bivalent and be defined as oxo or keto (thus forming a carbonyl group ($-CO-$) or as two separately attached monovalent variable substituents $\alpha-R_{i-j}$ and $\beta-R_{i-k}$. When a bivalent variable, R_i , is defined to consist of two monovalent variable substituents, the convention used to define the bivalent variable is of the form " $\alpha-R_{i-j}:\beta-R_{i-k}$ " or some variant thereof. In such a case both $\alpha-R_{i-j}$ and $\beta-R_{i-k}$ are attached to the carbon atom to give $-C(\alpha-R_{i-j})(\beta-R_{i-k})-$. For example, when the bivalent variable R_6 , $-C(=R_6)-$ is defined to consist of two monovalent variable substituents, the two monovalent variable substituents are $\alpha-R_{6-1}:\beta-R_{6-2}$, $\alpha-R_{6-9}:\beta-R_{6-10}$, etc, giving $-C(\alpha-R_{6-1})(\beta-R_{6-2})-$, $-C(\alpha-R_{6-9})(\beta-R_{6-10})-$, etc. Likewise, for the bivalent variable R_{11} , $-C(=R_{11})-$, two monovalent variable substituents are $\alpha-R_{11-1}:\beta-R_{11-2}$.

For a ring substituent for which separate α and β orientations do not exist (e.g. due to the presence of a carbon double bond in the ring), and for a substituent bonded to a carbon atom which is not part of a ring the above convention is still used, but the α and β designations are omitted.

Just as a bivalent variable may be defined as two separate monovalent variable substituents, two separate monovalent variable substituents may be defined to be taken together to form a bivalent variable. For example, in the formula $-C_1(R_i)H-C_2(R_j)H-$ (C_1 and C_2 define arbitrarily a first and second carbon atom, respectively) R_i and R_j may be defined to be taken together to form (1) a second bond between C_1 and C_2 or (2) a bivalent group such as oxa ($-O-$) and the formula thereby describes an epoxide. When R_i and R_j are taken together to form a more complex entity, such as the group $-X-Y-$, then the orientation of the entity is such that C_1 in the above formula is bonded to X and C_2 is bonded to Y . Thus, by convention the designation "... R_i and R_j are taken together to form $-CH_2-CH_2-O-CO-$..." means a lactone in which the carbonyl is bonded to C_2 . However, when designated "... R_j and R_i are taken together to form $-CO-O-CH_2-CH_2-$ the convention means a lactone in which the carbonyl is bonded to C_1 .

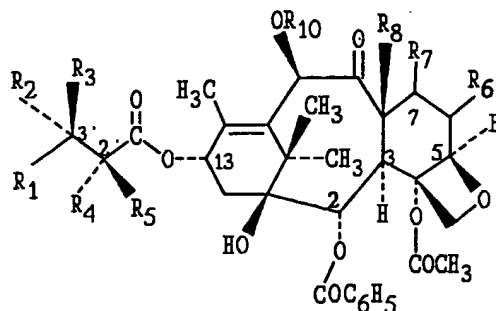
The carbon atom content of variable substituents is indicated in one of two ways. The first method uses a prefix to the entire name of the variable such as " C_1-C_4 ", where both "1" and "4" are integers representing the minimum and maximum number of carbon atoms in the variable. The prefix is separated from the variable by a space. For example, " C_1-C_4 alkyl" represents alkyl of 1 through 4 carbon atoms, (including isomeric forms thereof unless an express indication to the contrary is given). Whenever this single prefix is given, the prefix indicates the entire carbon atom content of the variable being defined. Thus C_2-C_4

alkoxycarbonyl describes a group $\text{CH}_3\text{-(CH}_2\text{)}_n\text{-O-CO-}$ where n is zero, one or two. By the second method the carbon atom content of only each portion of the definition is indicated separately by enclosing the "C₁-C_j" designation in parentheses and placing it immediately (no intervening space) before the portion of the definition being defined. By this optional convention (C₁-C₃)alkoxycarbonyl has the same meaning as C₂-C₄ alkoxycarbonyl because the "C₁-C₃" refers only to the carbon atom content of the alkoxy group. Similarly while both C₂-C₆ alkoxyalkyl and (C₁-C₃)alkoxy(C₁-C₃)alkyl define alkoxyalkyl groups containing from 2 to 6 carbon atoms, the two definitions differ since the former definition allows either the alkoxy or alkyl portion alone to contain 4 or 5 carbon atoms while the latter definition limits either of these groups to 3 carbon atoms.

When the claims contain a fairly complex (cyclic) substituent, at the end of the phrase naming/designating that particular substituent will be a notation in (parentheses) which will correspond to the same name/designation in one of the CHARTS which will also set forth the chemical structural formula of that particular substituent.

DETAILED DESCRIPTION OF THE INVENTION

More specifically, this invention provides 7-deoxy-taxol analogs of general Formula I



I

wherein:

30 R_1 is selected from the group consisting of
-CH₃,
-C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃
alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro,
-2-furyl, 2-thienyl, 1-naphthyl, 2-naphthyl or 3,4-methylenedioxyphenyl;
35 R_2 is selected from the group consisting of -H, -NHC(O)H, -NHC(O)C₁-C₁₀alkyl
(preferably -NHC(O)C₄-C₆alkyl), -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3

- C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro, -NHC(O)C(CH₃)=CHCH₃, -NHC(O)OC(CH₃)₃, -NHC(O)OCH₂phenyl, -NH₂, -NHSO₂-4-methylphenyl, -NHC(O)(CH₂)₃COOH, -NHC(O)-4-(SO₃H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl,
- 5 -NHC(O)CH₂C(CH₃)₃, -NHC(O)C(CH₃)₃, -NHC(O)OC₁-C₁₀alkyl, -NHC(O)NHC₁-C₁₀alkyl, -NHC(O)NHPh, -NHC(O)NHPh substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, or nitro, -NHC(O)C₃-C₈cycloalkyl, -NHC(O)C(CH₂CH₃)₂CH₃, -NHC(O)C(CH₃)₂CH₂Cl, -NHC(O)C(CH₃)₂CH₂CH₃, phthalimido, -NHC(O)-1-phenyl-1-cyclopentyl, -NHC(O)-1-methyl-1-cyclohexyl, -NHC(S)NHC(CH₃)₃,
- 10 -NHC(O)NHCC(CH₃)₃ or -NHC(O)NHPh;

R₃ is selected from the group consisting of -H, -NHC(O)phenyl or -NHC(O)OC(CH₃)₃, with the overall proviso that one of R₂ and R₃ is -H but R₂ and R₃ are not both -H;

- R₄ is -H or selected from the group consisting of -OH, -OAc (-OC(O)CH₃), -OC(O)OCH₂C(Cl)₃, -OCOCH₂CH₂NH₃⁺ HCOO⁻, -NHC(O)phenyl, -NHC(O)OC(CH₃)₃,
- 15 -OCOCH₂CH₂COOH and pharmaceutically acceptable salts thereof, -OCO(CH₂)₃COOH and pharmaceutically acceptable salts thereof, and -OC(O)-Z-C(O)-R' [where Z is ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), -CH=CH-, 1,2-cyclohexane or 1,2-phenylene, R' is -OH, -OH base, -NR'₂R'₃, -OR'₃, -SR'₃, -OCH₂C(O)NR'₄R'₅ where R'₂ is -H or -CH₃, R'₃ is -(CH₂)_nNR'₆R'₇ or (CH₂)_nN⁺R'₆R'₇R'₈ X⁻ where n is 1-3, R'₄ is -H or -C₁-C₄alkyl, R'₅ is -H,
- 20 -C₁-C₄alkyl, benzyl, hydroxyethyl, -CH₂CO₂H or dimethylaminoethyl, R'₆ and R'₇ are -CH₃, -CH₂CH₃, benzyl or R'₆ and R'₇ together with the nitrogen of NR'₆R'₇ form a pyrrolidino, piperidino, morpholino, or N-methylpiperizino group; R'₈ is -CH₃, -CH₂CH₃ or benzyl, X⁻ is halide, and base is NH₃, (HOC₂H₄)₃N, N(CH₃)₃, CH₃N(C₂H₄)₂NH, NH₂(CH₂)₆NH₂, N-methylglucamine, NaOH or KOH], -OC(O)(CH₂)_nNR²R³ [where n is 1-3, R² is -H or
- 25 -C₁-C₃alkyl and R³ is -H or -C₁-C₃alkyl], -OC(O)CH(R'')NH₂ [where R'' is selected from the group consisting of -H, -CH₃, -CH₂CH(CH₃)₂, -CH(CH₃)CH₂CH₃, -CH(CH₃)₂, -CH₂phenyl, -(CH₂)₄NH₂, -CH₂CH₂COOH, -(CH₂)₃NHC(=NH)NH₂], the residue of the amino acid proline, -OC(O)CH=CH₂, -C(O)CH₂CH₂C(O)NHCH₂CH₂SO₃⁻ Y⁺, -OC(O)CH₂CH₂C(O)NHCH₂CH₂CH₂SO₃⁻ Y⁺ wherein Y⁺ is Na⁺ or N⁺(Bu)₄,
- 30 -OC(O)CH₂CH₂C(O)OCH₂CH₂OH;

R₅ is -H or -OH, with the overall proviso that when R₅ is -OH, R₄ is -H and with the further proviso that when R₅ is -H, R₄ is other than -H;

R₆ is -H:-H when R₇ is α-R₇₁:β-R₇₂ where one of R₇₁ and R₇₂ is -H and the other of R₇₁ and R₇₂ is -X where X is halo and R₈ is -CH₃;

- 35 R₆ is -H:-H when R₇ is α-H:β-R₇₄ where R₇₄ and R₈ are taken together to form a cyclopropyl ring;

-7-

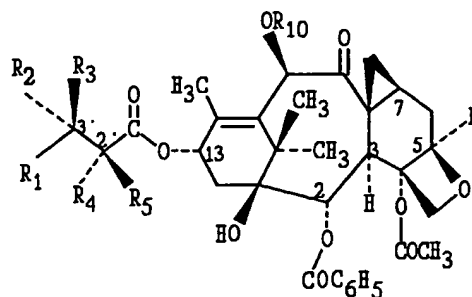
R_{10} is -H or -C(O)CH₃; and

pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic functional group.

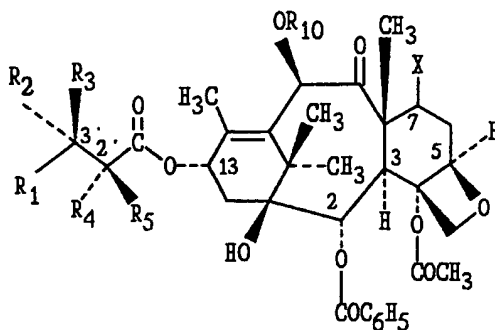
A preferred embodiment of the subject invention is compounds of Formula I where R_1 is phenyl or phenyl substituted with halo, R_2 is -NHC(O)C₆H₅, R_3 and R_5 are -H, R_4 is -OH, and R_{10} is -H or -C(O)CH₃. Another preferred embodiment of the subject invention is compounds of Formula I where R_1 is preferably phenyl or phenyl substituted with halo, R_2 is -NHC(O)OC(CH₃)₃, R_3 and R_5 are -H, R_4 is -OH, and R_{10} is -H or -COCH₃. A further preferred embodiment of the subject invention is compounds of Formula I where R_1 is preferably phenyl or phenyl substituted with halo, R_2 is -NHC(O)NHC(CH₃)₃, R_3 and R_5 are -H, R_4 is -OH, and R_{10} is -H or -COCH₃.

An embodiment of the subject invention are compounds of Formula I where R_1 is selected from the group consisting of -CH₃, -C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro and R_2 is selected from the group consisting of -H, -NHC(O)H, -NHC(O)C₁-C₁₀alkyl (preferably -NHC(O)C₄-C₆alkyl), -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro, -NHC(O)C(CH₃)=CHCH₃, -NHC(O)OC(CH₃)₃, -NHC(O)OCH₂phenyl, -NH₂, -NHSO₂-4-methylphenyl, -NHC(O)(CH₂)₃COOH, -NHC(O)-4-(SO₃H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl, -NHC(O)CH₂C(CH₃)₃, -NHC(O)C(CH₃)₃, -NHC(O)OC₁-C₁₀alkyl, -NHC(O)NHC₁-C₁₀alkyl, -NHC(O)NHPh substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, or nitro.

This invention also provides taxol analogs of general Formula II



and Formula III



wherein

X is a halogen atom selected from the group consisting of -F, -Br, -Cl and -I; and wherein R_1 , R_2 , R_3 , R_4 , R_5 and R_{10} are as defined above.

An embodiment of the present invention are 7-deoxy-7 β ,8 β -methano-taxol analogs of general Formula II wherein:

R_1 is selected from the group consisting of -CH₃, -C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro;

R_2 is selected from the group consisting of -H, -NHC(O)C₁-C₁₀alkyl (preferably -NHC(O)C₄-C₆alkyl), -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro, -NHC(O)C(CH₃)=CHCH₃, -NHC(O)OC(CH₃)₃, -NH₂, -NHSO₂-4-methylphenyl, -NHC(O)(CH₂)₃COOH, -NHC(O)-4-(SO₃H)phenyl, or -OH;

R_3 is selected from the group consisting of -H, -NHC(O)phenyl or -NHC(O)OC(CH₃)₃, with the overall proviso that one of R_2 and R_3 is -H but R_2 and R_3 are not both -H;

R_4 is -H or selected from the group consisting of -OH, -OAc (-OC(O)CH₃), -OC(O)OCH₂C(Cl)₃, -OCOCH₂CH₂NH₃⁺ HCOO⁻, -NHC(O)phenyl, -NHC(O)OC(CH₃)₃, -OCOCH₂CH₂COOH and pharmaceutically acceptable salts thereof, -OCO(CH₂)₃COOH and pharmaceutically acceptable salts thereof, and -OC(O)-Z-C(O)-R' [where Z is ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), -CH=CH-, 1,2-cyclohexane or 1,2-phenylene, R' is -OH, -OH base, -NR'₂R'₃, -OR'₃, -SR'₃, -OCH₂C(O)NR'₄R'₅ where R'₂ is -H or -CH₃, R'₃ is -(CH₂)_nNR'₆R'₇ or (CH₂)_nN⁺R'₆R'₇R'₈ X⁻ where n is 1-3, R'₄ is -H or -C₁-C₄alkyl, R'₅ is -H, -C₁-C₄alkyl, benzyl, hydroxyethyl, -CH₂CO₂H or dimethylaminoethyl, R'₆ and R'₇ are -CH₃, -CH₂CH₃, benzyl or R'₆ and R'₇ together with the nitrogen of NR'₆R'₇ form a pyrrolidino, piperidino, morpholino, or N-methylpiperizino group; R'₈ is -CH₃, -CH₂CH₃ or benzyl, X⁻ is

halide, and base is NH_3 , $(\text{HOC}_2\text{H}_4)_3\text{N}$, $\text{N}(\text{CH}_3)_3$, $\text{CH}_3\text{N}(\text{C}_2\text{H}_4)_2\text{NH}$, $\text{NH}_2(\text{CH}_2)_6\text{NH}_2$,
 N-methylglucamine, NaOH or KOH], $-\text{OC}(\text{O})(\text{CH}_2)_n\text{NR}^2\text{R}^3$ [where n is 1-3, R^2 is -H or
 - C_1 - C_3 alkyl and R^3 is -H or - C_1 - C_3 alkyl], $-\text{OC}(\text{O})\text{CH}(\text{R}'')\text{NH}_2$ [where R'' is selected from the
 group consisting of -H, $-\text{CH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)_2$, $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{phenyl}$,
 5 $-(\text{CH}_2)_4\text{NH}_2$, $-\text{CH}_2\text{CH}_2\text{COOH}$, $-(\text{CH}_2)_3\text{NHC}(=\text{NH})\text{NH}_2$], the residue of the amino acid proline,
 $-\text{OC}(\text{O})\text{CH}=\text{CH}_2$, $-\text{C}(\text{O})\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{SO}_3^- \text{Y}^+$,
 $-\text{OC}(\text{O})\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{NHCH}_2\text{CH}_2\text{CH}_2\text{SO}_3^- \text{Y}^+$ wherein Y^+ is Na^+ or $\text{N}^+(\text{Bu})_4$,
 $-\text{OC}(\text{O})\text{CH}_2\text{CH}_2\text{C}(\text{O})\text{OCH}_2\text{CH}_2\text{OH}$;

R_5 is -H or -OH, with the overall proviso that when R_5 is -OH, R_4 is -H and with the
 10 further proviso that when R_5 is -H, R_4 is other than -H;

R_{10} is -H or $-\text{C}(\text{O})\text{CH}_3$; and

pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic
 functional group.

Another embodiment of the present invention are 7-deoxy-7 β ,8 β -methano-taxol analogs
 15 of general Formula II wherein:

R_1 is selected from the group consisting of $-\text{CH}_3$, $-\text{C}_6\text{H}_5$ or phenyl substituted with one,
 2 or 3 C_1 - C_4 alkyl, C_1 - C_3 alkoxy, halo, C_1 - C_3 alkylthio, trifluoromethyl, C_2 - C_6 dialkylamino,
 hydroxy or nitro;

R_2 is selected from the group consisting of $-\text{NHC}(\text{O})$ -1-adamantyl, $-\text{NHC}(\text{O})$ O-3-
 20 tetrahydrofuranyl, $-\text{NHC}(\text{O})$ O-4-tetrahydropyranyl, $-\text{NHC}(\text{O})\text{CH}_2\text{C}(\text{CH}_3)_3$, $-\text{NHC}(\text{O})\text{C}(\text{CH}_3)_3$,
 $-\text{NHC}(\text{O})\text{OC}_1\text{-C}_{10}\text{alkyl}$, $-\text{NHC}(\text{O})\text{NHC}_1\text{-C}_{10}\text{alkyl}$, $-\text{NHC}(\text{O})\text{NHPh}$ substituted with one, 2 or 3
 C_1 - C_4 alkyl, C_1 - C_3 alkoxy, halo, C_1 - C_3 alkylthio, trifluoromethyl, C_2 - C_6 dialkylamino, or nitro,
 $-\text{NHC}(\text{O})\text{C}_3\text{-C}_8\text{cycloalkyl}$; and

R_3 , R_4 , R_5 and R_{10} are as defined above.

25 A preferred embodiment of the subject invention is compounds of Formula II where R_1
 is phenyl or phenyl substituted with halo, R_2 is $-\text{NHC}(\text{O})\text{C}_6\text{H}_5$, R_3 and R_5 are -H, and R_{10} is
 $-\text{C}(\text{O})\text{CH}_3$. Another preferred embodiment of the subject invention is compounds of Formula II
 where R_1 is preferably phenyl or phenyl substituted with halo, R_2 is $-\text{NHC}(\text{O})\text{OC}(\text{CH}_3)_3$, and
 R_3 , R_5 and R_{10} are -H. A further preferred embodiment of the subject invention is compounds
 30 of Formula II where R_1 is preferably phenyl or phenyl substituted with halo, R_2 is
 $-\text{NHC}(\text{O})\text{OC}(\text{CH}_3)_3$, and R_3 and R_5 are -H, and R_{10} is $-\text{C}(\text{O})\text{CH}_3$. Another preferred
 embodiment of the subject invention is compounds of Formula II where R_1 is preferably phenyl
 or phenyl substituted with halo, R_2 is $-\text{NHC}(\text{O})\text{NHC}(\text{CH}_3)_3$, R_3 and R_5 are -H, R_4 is -OH, and
 R_{10} is -H or $-\text{COCH}_3$.

35 Additional preferred embodiments of Formula II include:

- The compound according to Formula II, namely 7-deoxy-7 β ,8 β -methano-taxol;

-10-

- The compound according to Formula II, namely 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7 β ,8 β -methano-taxol; and
- The compound according to Formula II, namely 10-acetyl-7-deoxy-7 β ,8 β -methano-taxotere; and
- 5 - The compound according to Formula II, namely N-Debenzoyl-n-(*t*-butyl)aminocarbonyl-7-deoxy-7 β ,8 β -methano-taxol.

Another embodiment of the present invention are 7-halotaxol analogs of general Formula III wherein:

- X is a halogen atom selected from the group consisting of -F, -Br, -Cl and -I;
- 10 R_1 is selected from the group consisting of -CH₃, -C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro;
- R_2 is selected from the group consisting of -H, -NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl,
- 15 C₂-C₆ dialkylamino, hydroxy or nitro, -NHC(O)C(CH₃)=CHCH₃, -NHC(O)OC(CH₃)₃, -NH₂, -NHSO₂-4-methylphenyl, -NHC(O)(CH₂)₃COOH, -NHC(O)-4-(SO₃H)phenyl, or -OH;
- R_3 is selected from the group consisting of -H, -NHC(O)phenyl or -NHC(O)OC(CH₃)₃, with the overall proviso that one of R_2 and R_3 is -H but R_2 and R_3 are not both -H;
- R_4 is -H or selected from the group consisting of -OH, -OAc (-OC(O)CH₃),
- 20 -OC(O)OCH₂C(Cl)₃, -OCOCH₂CH₂NH₃⁺ HCOO⁻, -NHC(O)phenyl, -NHC(O)OC(CH₃)₃, -OCOCH₂CH₂COOH and pharmaceutically acceptable salts thereof, -CO(CH₂)₃COOH and pharmaceutically acceptable salts thereof, and -OC(O)-Z-C(O)-R' [where Z is ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), -CH=CH-, 1,2-cyclohexane or 1,2-phenylene, R' is -OH, -OH base, -NR'₂R'₃, -OR'₃, -SR'₃, -OCH₂C(O)NR'₄R'₅ where R'₂ is -H or -CH₃, R'₃ is
- 25 -(CH₂)_nNR'₆R'₇ or (CH₂)_nN⁺R'₆R'₇R'₈ X⁻ where n is 1-3, R'₄ is -H or -C₁-C₄alkyl, R'₅ is -H, -C₁-C₄alkyl, benzyl, hydroxyethyl, -CH₂CO₂H or dimethylaminoethyl, R'₆ and R'₇ are -CH₃, -CH₂CH₃, benzyl or R'₆ and R'₇ together with the nitrogen of NR'₆R'₇ form a pyrrolidino, piperidino, morpholino, or N-methylpiperizino group; R'₈ is -CH₃, -CH₂CH₃ or benzyl, X⁻ is halide, and base is NH₃, (HOC₂H₄)₃N, N(CH₃)₃, CH₃N(C₂H₄)₂NH, NH₂(CH₂)₆NH₂,
- 30 N-methylglucamine, NaOH or KOH], -OC(O)(CH₂)_nNR²R³ [where n is 1-3, R² is -H or -C₁-C₃alkyl and R³ is -H or -C₁-C₃alkyl], -OC(O)CH(R'')NH₂ [where R'' is selected from the group consisting of -H, -CH₃, -CH₂CH(CH₃)₂, -CH(CH₃)CH₂CH₃, -CH(CH₃)₂, -CH₂phenyl, -(CH₂)₄NH₂, -CH₂CH₂COOH, -(CH₂)₃NHC(=NH)NH₂], the residue of the amino acid proline, -OC(O)CH=CH₂, -C(O)CH₂CH₂C(O)NHCH₂CH₂SO₃⁻ Y⁺,
- 35 -OC(O)CH₂CH₂C(O)NHCH₂CH₂CH₂SO₃⁻ Y⁺ wherein Y⁺ is Na⁺ or N⁺(Bu)₄, -OC(O)CH₂CH₂C(O)OCH₂CH₂OH;

R_5 is -H or -OH, with the overall proviso that when R_5 is -OH, R_4 is -H and with the further proviso that when R_5 is -H, R_4 is other than -H;

R_{10} is -H or -C(O)CH₃; and

pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic functional group.

A further embodiment of the present invention are 7-halotaxol analogs of general Formula III wherein:

X is a halogen atom selected from the group consisting of -F, -Br, -Cl and -I;

R_1 is selected from the group consisting of -CH₃, -C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro;

R_2 is selected from the group consisting of -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl, -NHC(O)O-4-tetrahydropyranyl, -NHC(O)CH₂C(CH₃)₃, -NHC(O)C(CH₃)₃, -NHC(O)OC₁-C₁₀alkyl, -NHC(O)NHC₁-C₁₀alkyl, -NHC(O)NHPh substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, or nitro, -NHC(O)C₃-C₈cycloalkyl; and R_3 , R_4 , R_5 and R_{10} are as defined above.

The compounds of Formula III include both the 7- α and 7- β configuration of the 7-halo substitution. Halo refers to -F, -Br, -Cl or -I.

In compounds of Formula III: X is preferably -F, and R_3 and R_5 are preferably -H, and R_1 is preferably phenyl or phenyl substituted with halo.

Additional preferred embodiments of Formula III include:

- A compound according to Formula III wherein R_4 is -H and R_5 is -OH;
- A compound according to Formula III wherein R_4 is other than -H and R_5 is -H;
- A compound according to Formula III wherein R_3 is -H, and R_1 is Ph or substituted phenyl;
- A compound according to Formula III wherein X is -F;
- A compound according to Formula III wherein X is - α -F;
- A compound according to Formula III wherein X is -F and R_4 is other than -H and R_5 is -H;
- A compound according to Formula III wherein X is -F, R_3 is -H, and R_1 is Ph or substituted phenyl; and
- A compound according to Formula III selected from the group consisting of 7-deoxy-7-fluorotaxol and 2'-[(2,2,2-trichloroethyl)oxy]carbonyl-7-deoxy-7-fluorotaxol; and
- A compound according to Formula III, namely N-Debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7-fluoro-taxol.

An additional preferred embodiment of Formula III are compounds selected from the group consisting of 7-deoxy-7 α -fluorotaxol, 7-deoxy-7 β -fluorotaxol, 2'-[(2,2,2-trichloroethyl)-

oxy)carbonyl]-7-deoxy-7 α -fluorotaxol and 2'-[[(2,2,2-trichloroethyl)-oxy]carbonyl]-7-deoxy-7 β -fluorotaxol.

A preferred embodiment of the subject invention is compounds of Formula III where R₁ is preferably phenyl or phenyl substituted with halo, R₂ is -NHC(O)NHC(CH₃)₃, R₃ and R₅ are
 5 -H, R₄ is -OH, and R₁₀ is -H or -COCH₃.

Examples of -NHC(O)C₁-C₁₀alkyl include -NHC(O)-n-pentyl and
 -NHC(O)CH(CH₃)CH₂CH₃.

Examples of C₁-C₆ alkyl include straight and branched alkyl chains, including for
 example methyl, ethyl, isopropyl, t-butyl, isobutyl and 2-methyl-pentyl.

10 Examples of C₁-C₃ alkoxy are methoxy, ethoxy, propoxy and isomeric forms thereof
 Halo refers to -F, -Br, -Cl or -I.

Examples of Formula II compounds of this invention include:

2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7 β ,8 β -methano-taxol (Compound
 14AA, Compound IIa);

15 7-deoxy-7 β ,8 β -methano-taxol (Compound IIb);

2'-succinyl-7-deoxy-7 β ,8 β -methano-taxol;

2'-(β -alanyl)-7-deoxy-7 β ,8 β -methano-taxol formate;

2'-glutaryl-7-deoxy-7 β ,8 β -methano-taxol;

2'-[-C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7 β ,8 β -methano-taxol;

20 2'-(β -sulfopropionyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(2-sulfoethylamido)succinyl-7-deoxy-7 β ,8 β -methano-taxol;

2'-(3-sulfopropylamido)succinyl-7-deoxy-7 β ,8 β -methano-taxol;

2'-(triethylsilyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(t-butyl dimethylsilyl)-7-deoxy-7 β ,8 β -methano-taxol;

25 2'-(N,N-diethylaminopropionyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(N,N-dimethylglycyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(glycyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(L-alanyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(L-leucyl)-7-deoxy-7 β ,8 β -methano-taxol;

30 2'-(L-isoleucyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(L-valyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(L-phenylalanyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(L-prolyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(L-lysyl)-7-deoxy-7 β ,8 β -methano-taxol;

35 2'-(L-glutamyl)-7-deoxy-7 β ,8 β -methano-taxol;

2'-(L-arginyl)-7-deoxy-7 β ,8 β -methano-taxol;

- 7-deoxy-7 β ,8 β -methano-taxotere;
 10-acetyl-7 β ,8 β -methano-taxotere (Compound 23);
 N-Debenzoyl-N-tetrahydrofuran-3-yloxy carbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(1-adamantoyl)-7-deoxy-7 β ,8 β -methanotaxol;
 5 N-Debenzoyl-N-phenylaminocarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-t-butylaminocarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(1-methyl-1-cyclohexyl)anoyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(1-phenyl-1-cyclopentyl)anoyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-phthalimido-7-deoxy-7 β ,8 β -methanotaxol;
 10 N-Debenzoyl-N-t-butylaminothiocarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-t-amylloxycarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-neopentylloxycarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(2-chloro-1,1-dimethylethyl)oxycarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(3-methyl-3-pentyl)oxycarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 15 3'-desphenyl-3'-(2-furyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(2-thienyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(1-naphthyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(2-naphthyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
 20 3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(4-bromophenyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(3,4-methylenedioxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(3,4-dimethoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(4-nitrophenyl)-7-deoxy-7 β ,8 β -methanotaxol;
 25 3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;
 N-debenzoyl-N-(4-bromobenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
 N-debenzoyl-N-(4-methylbenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
 N-debenzoyl-N-(4-t-butylbenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
 N-debenzoyl-N-(4-methoxybenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
 30 N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -
 methanotaxol;
 N-debenzoyl-N-(4-fluorobenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
 N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -
 methanotaxol;
 35 N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -
 methanotaxol;

N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;

N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;

5 N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;

N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;

10 N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;

N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;

N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;

15 N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;

N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;

20 N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;

N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;

N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;

25 N-debenzoyl-N-(4-methoxybenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;

N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7 β ,8 β -methano-taxol (Compound 29);

and

pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic
30 functional group.

Examples of Formula III compounds of this invention include:

2'-[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7-fluorotaxol (Compound 13AA, IIIc);
7-deoxy-7-fluorotaxol (Compound IIIb);

2'-succinyl-7-deoxy-7-fluorotaxol;

35 2'-(β -alanyl)-7-deoxy-7-fluorotaxol formate;

2'-glutaryl-7-deoxy-7-fluorotaxol;

- 2'-[-C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7-fluorotaxol;
2'-(β-sulfopropionyl)-7-deoxy-7-fluorotaxol;
2'-(2-sulfoethylamido)succinyl-7-deoxy-7-fluorotaxol;
2'-(3-sulfopropylamido)succinyl-7-deoxy-7-fluorotaxol;
5 2'-(triethylsilyl)-7-deoxy-7-fluorotaxol;
2'-(*t*-butyldimethylsilyl)-7-deoxy-7-fluorotaxol;
2'-(*N,N*-diethylaminopropionyl)-7-deoxy-7-fluorotaxol;
2'-(*N,N*-dimethylglycyl)-7-deoxy-7-fluorotaxol;
2'-(glycyl)-7-deoxy-7-fluorotaxol;
10 2'-(*L*-alanyl)-7-deoxy-7-fluorotaxol;
2'-(*L*-leucyl)-7-deoxy-7-fluorotaxol;
2'-(*L*-isoleucyl)-7-deoxy-7-fluorotaxol;
2'-(*L*-valyl)-7-deoxy-7-fluorotaxol;
2'-(*L*-phenylalanyl)-7-deoxy-7-fluorotaxol;
15 2'-(*L*-prolyl)-7-deoxy-7-fluorotaxol;
2'-(*L*-lysyl)-7-deoxy-7-fluorotaxol;
2'-(*L*-glutamyl)-7-deoxy-7-fluorotaxol;
2'-(*L*-arginyl)-7-deoxy-7-fluorotaxol;
7-deoxy-7-fluorotaxotere;
20 10-acetyl-7-deoxy-7-fluorotaxotere (Compound 20);
N-Debenzoyl-N-tetrahydropyran-4-yloxycarbonyl-7-deoxy-7-fluorotaxol;
N-Debenzoyl-N-pivaloyl-7-deoxy-7-fluorotaxol;
N-Debenzoyl-N-*n*-hexylaminocarbonyl-7-deoxy-7-fluorotaxol;
N-Debenzoyl-N-*t*-butylaminocarbonyl-7-deoxy-7-fluorotaxol;
25 N-Debenzoyl-N-(1-methyl-1-cyclohexylanoyl)-7-deoxy-7-fluorotaxol;
N-Debenzoyl-N-(1-phenyl-1-cyclopentanoyl)-7-deoxy-7-fluorotaxol;
N-Debenzoyl-N-phthalimido-7-deoxy-7-fluorotaxol;
N-Debenzoyl-N-*t*-butylaminothiocarbonyl-7-deoxy-7-fluorotaxol;
N-Debenzoyl-N-*t*-amyloxycarbonyl-7-deoxy-7-fluorotaxol;
30 N-Debenzoyl-N-neopentylloxycarbonyl-7-deoxy-7-fluorotaxol;
N-Debenzoyl-N-(2-chloro-1,1-dimethylethyl)oxycarbonyl-7-deoxy-7-fluorotaxol;
N-Debenzoyl-N-(3-methyl-3-pentyl)oxycarbonyl-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(2-furyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(2-thienyl)-7-deoxy-7-fluorotaxol;
35 3'-desphenyl-3'-(1-naphthyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(2-naphthyl)-7-deoxy-7-fluorotaxol;

- 3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(4-bromophenyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(3,4-methylenedioxyphenyl)-7-deoxy-7-fluorotaxol;
5 3'-desphenyl-3'-(3,4-dimethoxyphenyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(4-nitrophenyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-bromobenzoyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-methylbenzoyl)-7-deoxy-7-fluorotaxol;
10 N-debenzoyl-N-(4-t-butylbenzoyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-methoxybenzoyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-
fluorotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-7-deoxy-7-fluorotaxol;
15 N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-
fluorotaxol;
N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-
fluorotaxol;
N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-
20 fluorotaxol;
N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-
fluorotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-
fluorotaxol;
25 N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-
fluorotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-
fluorotaxol;
N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-
30 fluorotaxol;
N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-
fluorotaxol;
N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-
fluorotaxol;
35 N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-
fluorotaxol;

-17-

N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;

N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;

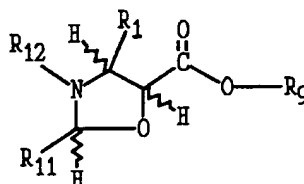
5 N-debenzoyl-N-(4-*t*-butylbenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;

N-debenzoyl-N-(4-methoxybenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;

N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7-fluoro-taxol (Compound 28); and
10 pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic functional group.

The present invention also provides a process for preparing oxazolidines of Formula 5

15



in which

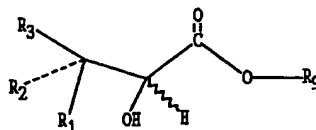
20 R_1 is as defined above;

R_9 is selected from C_1 - C_6 alkyl; R_{11} is phenyl substituted with $-(OC_1-C_2\text{alkyl})_n$ where n is 1 to 3;

R_{12} is selected from the group consisting of $-C(O)H$, $-C(O)C_1-C_{10}$ alkyl (preferably $-C(O)C_4-C_6$ alkyl), $-C(O)$ phenyl, $-C(O)$ phenyl substituted with one, 2 or 3 C_1-C_4 alkyl,
25 C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, $-C(O)C(CH_3)=CHCH_3$, $-C(O)OC(CH_3)_3$, $-C(O)OCH_2$ phenyl, $-SO_2$ -4-methylphenyl, $-C(O)(CH_2)_3COOH$, $-C(O)$ -4-(SO_3H)phenyl, $-C(O)$ -1-adamantyl, $-C(O)O$ -3-tetrahydrofuranyl, $-C(O)O$ -4-tetrahydropyranyl, $-C(O)CH_2C(CH_3)_3$, $-C(O)C(CH_3)_3$, $-C(O)OC_1-C_{10}$ alkyl, $-C(O)NHC_1-C_{10}$ alkyl, $-C(O)NHPh$ substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo,
30 C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, or $-C(O)C_3-C_8$ cycloalkyl, $-C(O)C(CH_2CH_3)_2CH_3$, $-C(O)C(CH_3)_2CH_2Cl$, $-C(O)C(CH_3)_2CH_2CH_3$, $-C(O)$ -1-phenyl-1-cyclopentyl, $-C(O)$ -1-methyl-1-cyclohexyl, $-C(S)NHC(CH_3)_3$, $-C(O)NHCC(CH_3)_3$ or $-C(O)NHPh$;

-18-

which comprises reacting a hydroxy-amine of Formula 3

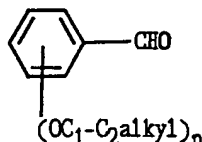


5

in which R_1 and R_3 are as defined above and R_2 is selected from the group consisting of
 -NHC(O)H, -NHC(O) C_1 - C_{10} alkyl (preferably -NHC(O) C_4 - C_6 alkyl), -NHC(O)phenyl,
 -NHC(O)phenyl substituted with one, 2 or 3 C_1 - C_4 alkyl, C_1 - C_3 alkoxy, halo, C_1 - C_3 alkylthio,
 10 trifluoromethyl, C_2 - C_6 dialkylamino, hydroxy or nitro, -NHC(O) $C(CH_3)=CHCH_3$,
 -NHC(O)OC(CH₃)₃, -NHC(O)OCH₂phenyl, -NHSO₂-4-methylphenyl, -NHC(O)(CH₂)₃COOH,
 -NHC(O)-4-(SO₃H)phenyl, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl,
 -NHC(O)O-4-tetrahydropyranyl, -NHC(O)CH₂C(CH₃)₃, -NHC(O)C(CH₃)₃,
 -NHC(O)OC $_1$ - C_{10} alkyl, -NHC(O)NHC $_1$ - C_{10} alkyl, -NHC(O)NHPh substituted with one, 2 or 3
 15 C_1 - C_4 alkyl, C_1 - C_3 alkoxy, halo, C_1 - C_3 alkylthio, trifluoromethyl, C_2 - C_6 dialkylamino, or nitro,
 or -NHC(O) C_3 - C_8 cycloalkyl, -NHC(O)C(CH₂CH₃)₂CH₃, -NHC(O)C(CH₃)₂CH₂Cl,
 -NHC(O)C(CH₃)₂CH₂CH₃, -NHC(O)-1-phenyl-1-cyclo-pentyl, -NHC(O)-1-methyl-1-cyclohexyl,
 -NHC(S)NHC(CH₃)₃, -NHC(O)NHCC(CH₃)₃ or -NHC(O)NHPh;

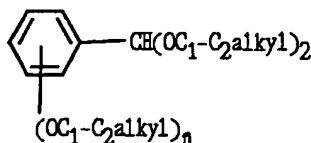
with (1) an electron rich benzaldehyde of Formula 4A

20



25

or (2) an electron rich acetal of Formula 4



30

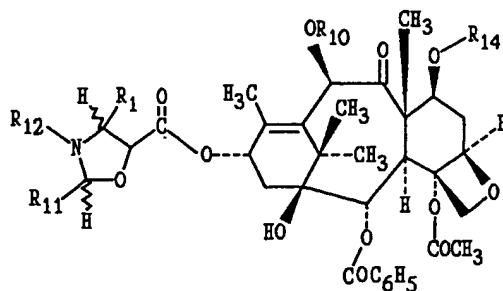
where n is 1-3.

35

-19-

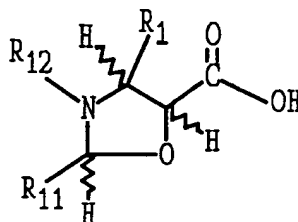
In addition, the present invention provides a process of preparing

5



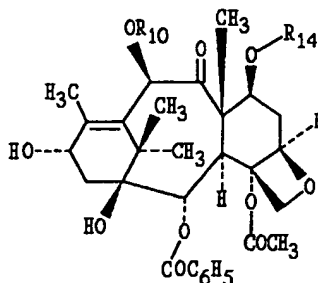
10 which comprises reacting an oxazolidine free acid of Formula 7

15



with a baccatin compound of Formula 8

20



25

in the presence of a dehydrating agent. Wherein R_{10} and R_{14} , being the same or different, are selected from the group consisting of $-C(O)C_1-C_6\text{alkyl}$ (preferably $-C(O)CH_3$), $-C(O)OC_1-C_6\text{alkyl}$, $-C(O)OCH_2CX_3$ where X is Halo, $-C(O)OCH_2CH_2SiR_{20}$ (where R_{20} is $C_1-C_6\text{alkyl}$), or $-Si(R_{20})_3$; R_{11} and R_{12} are as defined above.

30

The compounds of the present invention are prepared by the method(s) as shown in Charts A, A', B and C.

The starting point for the method shown in Chart A is a taxol or taxol analog derivative A-1. Reaction of the A-1 compound with a reagent such as diethylaminosulfur trifluoride (DAST), dimethylaminosulfur trifluoride (methylDAST), bis(dimethylamino)sulfur difluoride, bis(diethylamino)sulfur difluoride, or (diethylamino)(dimethylamino)sulfur difluoride, gives the

35

7-deoxy-7 β ,8 β -methano analog A'-2 (CHART A-II) as well as 7-deoxy-7-fluoro analog A"-2 (CHART A-III). The preferred method for this conversion is with DAST or methylDAST. The reaction with DAST or methylDAST is carried out in an aprotic solvent such as methylene chloride (CH₂Cl₂), chloroform (CHCl₃), fluorotrichloromethane (Freon 11[®]), ethylene glycol dimethyl ether (glyme), 2-methoxyethyl ether (diglyme), pyridine, hydrocarbons such as pentane, hexane, or isooctane, tetrahydrofuran (THF), benzene, toluene, xylene. The preferred solvent is methylene chloride. The reaction may be performed in a range of temperature from -100°C to 100°C or above. Generally, the reaction is begun under conditions of low temperature, *e.g.*, -78°C, and then is allowed to proceed at a higher temperature, *e.g.*, 25°C. The reaction is quenched with water, the crude product is isolated by standard extraction methods, and is purified by standard chromatographic methods and/or by crystallization. [When R₄ is -OC(O)OCH₂C(Cl)₃, treatment of A'-2 (CHART A-II) with activated zinc in methanol-acetic acid solution will serve to remove the protecting group and produce the desired 7-deoxy-7 β , β -methano-taxol or 7-deoxy-7 β , β -methano-taxol analog A'-3 (CHART A-II). When R₄ is -OC(O)OCH₂C(Cl)₃, treatment of A"-2 (CHART A-III) with activated zinc in methanol-acetic acid solution will serve to remove the protecting group and produce the desired 7-deoxy-7-fluorotaxol or 7-deoxy-7-fluorotaxol analog A"-3 (CHART A-III).] Methodologies for the addition of various protecting groups to taxol or to taxol analogs and for the removal of such groups are found in: Greene, T.W. and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd Ed., pages 10-142, Wiley, N.Y. 1991.

Alternatively, the compounds (Formula II) of this invention may be prepared treatment of a 7-epi taxol derivative with DAST in dichloromethane as disclosed in Chen et al., Serendipitous Synthesis of a Cyclopropane-Containing Taxol Analog via Anchimeric Participation of an Unactivated Angular Methyl Group, *Advance ACS Abstracts*, Vol 1, No. 2., July 15, 1993 and *J. Org. Chem.*, 1993, 56, 4520, (August 13, 1993).

The compounds (Formula II) of this invention may also be prepared by the method shown in Chart B-II. In this method, when Z' = H in Formula II (when Z' = H; R₁₀ = -C(O)CH₃, this Formula II structure is also known as baccatin III), treatment of baccatin III or a suitably protected (Z' = troc) baccatin III molecule B-1 by the method described above will produce 7-deoxy-7 β ,8 β -methano-baccatin III (B-2) after removal of the protecting group. Reaction of B-2 with an activated side chain precursor B-3 by one of several methods described in the literature (see: Kingston, D. G. I. *Pharmac. Ther.*, 1991, 52, 1-34; Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.*, 1992, 33, 5185; Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R. *BioMed. Chem. Lett.* 1992, 2, 295) gives B-4. For example, coupling of 7-deoxy-7 β ,8 β -methano-baccatin III with (4S,5R)-N-BOC-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid followed by subsequent transformation

according to the procedures of Commerçon, *et.al.*, gives an intermediate that is useful for further transformations into 7-deoxy-7 β ,8 β -methano-taxol, 7-deoxy-7 β ,8 β -methano-taxotere [compound of formula II, wherein R₁=Ph;

R₂ = NHC(O)O-*t*-Bu; R₃ = R₅ = H; R₄ = R₆ = OH;], and other 7-deoxy-7 β ,8 β -methano-
5 taxol analogs.

The compounds (Formula II) of this invention may also be prepared from taxol or taxol analogs having a substituent at C-7 with the properties of a good leaving group, e.g., (a) a diazonium ion precursor such as -NH₂, (b) a sulfonate ester, -OSO₂R (where R is a group such as, for example, -CH₃, -CF₃, C₆H₄-(p)-CH₃, -C₆H₄-(p)-Br, -C₆H₄-(p)-NO₂, or (c) one of the
10 halogens, iodine or bromine (-I or -Br). A C-7 amine substituent upon reaction with nitrous acid (HNO₂) is converted to a diazonium ion. The diazonium ion undergoes spontaneous loss of nitrogen resulting in formation of the 7 β ,8 β -methano functional group. A C-7 sulfonate ester when dissolved in a polar solvent (such as methanol-water, ethanol-water, trifluoroacetic acid) undergoes ionization resulting in formation of the 7 β ,8 β -methano functional group. The
15 ionization of the C-7 sulfonate ester may be enhanced by the addition of a non-nucleophilic base [such as potassium carbonate, potassium bicarbonate, 1,4-diazabicyclo [2.2.2] octane (DABCO)] to the reaction medium. A C-7 iodide or bromide undergoes ionization and formation of the 7 β ,8 β -methano functional group in a polar solvent in the presence of metal salts, particularly silver salts such as silver acetate, silver trifluoroacetate, silver tetrafluoro-borate.

20 The compounds (Formula III) of this invention may also be prepared by the method shown in Chart B-III. In this method, when Z' = H in Formula II (when Z' = H; R₁₀ = -COCH₃, this Formula II structure is also known as baccatin III), fluorination of baccatin III or a suitably protected (Z' = troc) baccatin III molecule B-1 by the method described above will produce 7-fluorobaccatin III (B-2) after removal of the protecting group. Reaction of B-2 with
25 an activated side chain precursor B-3 by one of several methods described in the literature (see: Kingston, D. G. I. *Pharmac. Ther.*, 1991, 52, 1-34; Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.*, 1992, 33, 5185; Georg, G. I.; Cheruvallath, Z. S.; Himes, R. H.; Mejillano, M. R. *BioMed. Chem. Lett.* 1992, 2, 295) gives B-4. For example, coupling of 7-fluorobaccatin III with (4S,5R)-N-BOC-2,2-dimethyl-4-phenyl-5-oxazolidinecarboxylic acid
30 followed by subsequent transformation according to the procedures of Commerçon, *et.al.*, gives an intermediate that is useful for further transformations into 7-deoxy-7-fluorotaxol, 7-deoxy-7-fluorotaxotere [compound of formula III, wherein R₁=Ph; R₂ = NHC(O)O-*t*-Bu; R₃ = R₅ = H; R₄ = OH; R₁₀ = -C(O)CH₃], and other 7-deoxy-7-fluorotaxol analogs.

The compounds (Formula I including Formula II and III) of this invention may be
35 prepared by a new, improved procedure as shown in Charts A', B and C. The preparation of 3-azido-2-hydroxy-carboxylic acid esters 1 may be prepared as described in the literature (see

Denis, J-N.; Correa, A.; Greene, A. E. *J. Org. Chem.*, 1990, 55, 1957). These materials are readily hydrogenated to the free amines 2, even though the literature intentionally avoids this intermediate by preparing the hydroxy-acylated intermediate prior to the reduction of the azide. The amine 2 is sufficiently stable that no problem is encountered in isolating it and directly using it to prepare the N-acylated free hydroxy compounds 3. Compounds 3 have been utilized by protection of the hydroxy group, hydrolysis of the ester to the acid, and condensation directly with a baccatin III derivative or after conversion to the oxazinone (European Patent 0 428 376 A1, US 436235). These procedures are distinctly inferior because they require large excesses of the acylating agent and generally do not proceed beyond about 60% completion. Procedures have also been described using a beta-lactam intermediate but these also require large excesses of reagent or the introduction of very strong bases such as LDA which makes them more difficult to perform and unsuitable for certain analogs (Ojima, I.; Habus, I.; Zhao, M.; George, G. I.; Jayasinghe, L. R. *J. Org. Chem.*, 1991, 56, 1681, EP 0 400 971 A2). A very effective condensation procedure involving the conversion of the hydroxy-amine derivative 3 to an oxazolidine with 2 non hydrogen substituents at the 2 position was described by Commerçon, A.; Bézard, D.; Bernard, F.; Bourzat, J. D. in *Tetrahedron Lett.*, 1992, 33, 5185 and Patent WO 92/09589. The condensation proceeds in very high yield but the removal of the protecting group requires sufficiently strong acid that sensitive taxol analogs are destroyed under the deprotection conditions. We have modified and improved this procedure by formation of the oxazolidines 5 not with a ketone, as the above workers have used but, with an electron rich benzaldehyde 4. The oxazolidines derived from the benzaldehyde 4 are produced as a mixture of diastereomers but these have been separated in some cases and the diastereomers have been shown to be equally useful when carried on in the synthesis. The oxazolidines 5 are readily hydrolyzed to the salts 6 and the acids 7. The acid is labile and needs to be used shortly after preparation. Both oxazolidine isomers are equally effective in the condensation reaction with the protected baccatins 8 giving an excellent yield of the oxazolidine protected taxol analogs 9. More importantly, both oxazolidine isomers from these electron rich benzaldehydes are readily hydrolyzed under very mild acid conditions allowing deprotection without causing undesired transformations of highly acid sensitive taxol derivatives such as 10 which are the subject of this invention. There are references to the use of electron rich aldehydes for the protection of 1,2-diols as dioxolanes but no previous reference to the use of such aldehydes for the protection of 2-hydroxy protected amines. The deprotection may be carried out such that both the oxazolidine and the 7 protected hydroxyl of 9 are removed at the same time or each may be removed independently. Additionally described is the deprotection of selected urethane analogs 10 to the free amine 11 (Chart B). These are then reconverted to a variety of amine acylated analogs 10.

The conversion of azide 1 to the amine 2 is effected by reduction as is known in the art.

Thus, the reaction may be carried out by hydrogenation in the presence of a variety of hydrogenation catalysts such as palladium, platinum, rhodium, or ruthenium. Alternatively, the azide may be reduced by treatment with a phosphine such as triphenyl or tributyl phosphine or by an acid such as hydrochloric, sulfuric, trifluoroacetic or hydrobromic in the presence of a metal such as zinc, iron, or tin. These reactions may be effected in a solvent such as ethanol, methanol, ethyl acetate, methyl t-butyl ether or tetrahydrofuran and the like. The conversion of amine 2 to its acylated derivative 3 is effected by treatment of the amine in pyridine or a non-basic solvent such as methylene chloride or tetrahydrofuran containing a tertiary amine such as triethyl amine or ethyl diisopropyl amine with an acylation agent. If 3 is a urethane, 2 is treated with an agent such as benzylchloroformate, 2,2,2-trichloroethoxycarbonyl chloride, di-tert-butylidicarbonate, or other urethane forming agent as is known in the art. If 3 is an amide, 2 is treated with an acylating agent such as an acyl halide, and acyl anhydride, or other acylating agent as is known in the art. If 3 is a urea or a thiourea, 2 is treated with an agent such as alkyl or aryl isocyanate, alkyl or aryl isothiocyanate, or other urea or thiourea forming agent as is known in the art.

The hydroxy amide or urethane 3 is converted to the oxazolidine 5 by treatment with an electron rich benzaldehyde or its acetal such as dimethyl or diethyl acetal 4 and an acid catalyst such as p-toluene sulfonic acid, pyridinium p-toluene sulfonate or other acid catalysts known in the art in a solvent such as tetrahydrofuran, toluene, methylene chloride, or other aprotic solvent. Examples of electron rich benzaldehydes include but are not limited to 2-, 3-, 4-methoxybenzaldehyde; 2,4-, 3,5-, 2,5-dimethoxybenzaldehyde; 2,4,6-trimethoxybenzaldehyde; and 4-ethoxybenzaldehyde. The preferred benzaldehyde is 2,4-dimethoxybenzaldehyde. The oxazolidine formation is generally carried out by heating to reflux to distill both the solvent and to carry off the evolved water or alcohol. The ester of 5 is hydrolyzed to the salt 6 by treatment with an alkali or quaternary amine hydroxide or by an alkali carbonate or other base as known in the art in a solvent such as water, methanol, ethanol, or other protic solvent. The reaction may be carried out from -78°C to 100°C. The product 6 is stable and may be isolated by evaporation of the solvents and stored as a solid or the reaction may be used directly to convert 6 to the acid 7 by treatment with acid. Generally, 7 is obtained by treating an aqueous solution of 6 in a separatory funnel with sufficient acid such as hydrochloric, sulfuric, potassium hydrogen sulfate, or the like, and partitioning the desired acid into an organic solvent such as ethyl acetate, methylene chloride, ether, or the like and evaporation of the solvent. The resultant acid 7 is sufficiently pure and stable for use in the next reaction but in general is not sufficiently stable for long term storage. The acid 7 is condensed with the baccatin derivative 8 to form the ester 9 with a dehydrating agent. Most preferred for this procedure is a carbodiimide such as dicyclohexyl carbodiimide, diisopropyl carbodiimide, di-p-tolyl carbodiimide, ethyl

dimethylaminopropyl carbodiimide hydrochloride salt, or the like, and a basic catalyst, preferably 4-dimethylaminopyridine. The reaction is generally carried out in an aprotic solvent such as toluene, benzene, tetrahydrofuran, dioxane, or the like at 25°C to 100°C. Other dehydration procedures for the formation of 9 may be used such as conversion of 7 to its mixed ester with a sulfonic acid such as with toluenesulfonyl chloride or benzenesulfonyl chloride, or formation of the acid halide from the dried 6 in the presence of oxalyl chloride as is known in the art for acid sensitive carboxylic acids. The oxazolidines 9 may be deprotected so that the protecting oxazolidine and the groups blocking the hydroxyl at the baccatin 7 position are individually removed in either order or both removed together depending on the protecting group at the 7 position and on the reaction conditions. If R_{14} is an acid labile group such as a silyl ether, then hydrolysis of the oxazolidine may be run under mild acid conditions and leads to the 7 position deprotection as well, giving 10MZ directly. Conditions for such conversions include hydrolysis in aqueous acetic acid, aqueous alcoholic acid of 0.01 to 0.1 N at 0°C to 50°C, or alcoholic acid of 0.01 to 0.1 N at 0°C to 50°C. Alternatively, the protection at the 7 position could be removed at a second step if it is not acid labile. For example, the trichloroethoxycarbonyl group at position 7 could be removed from 10MY (Chart B) by reduction as is known in the art to give 10MZ. Depending on the nature of the protecting group on the nitrogen (i.e. R_2 or R_3) of 10MZ (Chart B) the protecting group can be removed to give 11Z. For example, when R_2 is $\text{PhCH}_2\text{OC(O)NH}$, it may be removed by mild hydrogenolysis. Conditions for such conversions include reduction with hydrogen over a metal catalyst such as palladium in a solvent such as ethanol or ethyl acetate at room temperature and from one to three atmospheres of pressure. Other methods are known in the art. The resultant amine 11Z may be reconverted to an amide or urethane 10MZ (Chart B) by acylation procedures as described for the conversion of 2 to 3 above. The product 10MZ may be protected on the 2' hydroxyl to give 12MZ (Chart B). For example, the 2' hydroxyl may be acylated with trichloroethoxycarbonyl chloride in pyridine or other aromatic amine solvents, or in a non basic solvent such as toluene, methylene chloride, or tetrahydrofuran containing a tertiary amine base. The reaction may be run at -50°C to 100°C. Other methods for such acylations are well known in the art.

30 The reaction of taxol, taxol analogs 10MZ (R_{15} is acetate or other suitable acyl moiety), baccatin III, or baccatin III analogs 8 (R_6 is acetate or other suitable acyl moiety) with hydrazine comprises a particularly advantageous method for preparation of 10-deacetyl taxol, 10-deacetyl taxol analogs (10MZ, $R_{15} = \text{H}$), 10-deacetyl baccatin III, and 10-deacetyl baccatin III analogs (8, $R_6 = \text{H}$). Whereas the reported method (Samaranayake, G.; *et. al.*, *J. Org. Chem.*, 1991, 56, 5114) for removal of the acyl group from this position of taxol and baccatin structures, i.e., zinc bromide in methanol, gives a number of other products in addition to the desired deacylation

NO. 2 product, the reaction with hydrazine gives almost exclusively the desired deacylation product. The reaction may be performed at room temperature in an organic solvent and usually requires as little time as 15 min or as much as 24 hr, depending on the substrate. The preferred solvent for the reaction is 95% ethanol and 98% hydrazine is the preferred form of the reagent.

5 Preparation No. 1: Preparation of (2R,3S)- β -phenyl isoserine methyl ester (2)

The (2R,3S)-3-azido-2-hydroxy-3-phenylpropionic acid methyl ester (1, 0.5 g) is hydrogenated over 10% palladium on carbon (0.1 g) in ethanol at atmospheric pressure for 1 hour. The reaction is filtered and evaporated to yield the desired amine. Mp 106-108°C.

NMR(CDCl₃, TMS): δ 2.1 (bs); 3.80 (s, 3H); 4.31 (m, 2H); 7.28-7.45 (m, 5H).

10 Preparation No. 2: Preparation of (4S,5R)-N-Benzoyl-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (5Aa & 5Ab)

N-Benzoyl- β -phenyl isoserine methyl ester (3A, 0.5 g, 1.67 mM) is dissolved in dry THF (10 mL) and benzene (10 mL) and the solution treated with 2,4-dimethoxy benzaldehyde dimethyl acetal (4, 0.420 g, 1.98 mM) and pyridinium p-toluenesulfonate (12 mg) and the
15 solution warmed to reflux. After 30 minutes the reaction is cooled to RT and allowed to stand overnight. It is then again warmed to slowly distill off 1/2 of the solvent over 1 hr. TLC shows the reaction to be finished at this point. The reaction is concentrated in vacuo and the residue chromatographed over 50 g silica gel packed in (5-95) methanol-toluene. The column is eluted with methanol-toluene (5-95). Fractions of 12 mL are collected. The product elutes as a
20 mixture. Thus, fractions containing both 5Aa & 5Ab are recombined and evaporated. The residue (0.90 g) is rechromatographed over silica gel (100 g) The column is eluted with ethyl acetate-toluene (500 mL of 15-85 and 500 mL of 20-80). Fractions of 20 mL are collected and analyzed by TLC. The fractions containing each 5Aa & 5Ab are combined and evaporated under vacuum.

25 less polar isomer 5Aa
mixture of less polar and more polar isomers 5Aa and 5Ab
more polar 5Ab

Isomer 5Ab is crystallized from EtOAc to give white crystals (142 mg, mp 138-141°C).

30 Data for 5Aa:

TLC: silica gel; 20% EtOAc-80% toluene; R_f: 0.50

¹H NMR (CDCl₃; TMS): δ ; 3.69 (s, 3H); 3.77 (s, 3H); 3.86 (s, 3H); 4.93 (d, 1H); 5.6 (brs, 1H); 6.28-6.37 (m, 2H); 6.90 (s, 1H); 7.03 (d, 1H); 7.15-7.55 (m, 9);.

Data for 5Ab:

35 TLC: silica gel; 20% EtOAc-80% toluene; R_f: 0.41.

¹H NMR (CDCl₃; TMS): δ 3.62 (bs, 3H); 3.75 (brs, 6H); 4.65 (d, 1H); 5.68 (bs, 1H);

6.2-6.5 (m, 2H); 6.8-7.55 (m, 11H).

UV: EtOH; 229 (16,000), 277 (3,240), 281sh (3,170).

Elemental analysis: Calculated: C 69.79; H 5.63; N 3.13.

Found: C 69.61; H 5.61; N 2.93.

- 5 Preparation No. 3: Preparation of (4S,5R)-N-benzyl-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid potassium salt. **6Ab**

(4S,5R)-N-benzyl-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid methyl ester (Preparation No. 2, **5Ab**, 355mg, 0.79 mM) is dissolved in 9mL methanol. To the solution is added water (350 μ l) and potassium carbonate (155 mg, 1.12mM). After stirring 5
10 hours no solids remain and TLC indicates very little methyl ester remaining. The solvent is concentrated in vacuo and water (10ml) added to the oil. The solution is freeze dried leaving 500 mg fluffy white powder which contains 374 mg of the potassium salt.

TLC: silica gel 60; 1:2 EtOAc:Hexane; R_f : origin.

- Preparation No. 4: Preparation of 7-TES-baccatin III-13-(4S,5R)-N-Benzoyl-2-(2,4-
15 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (**9AbA**)

A solution of (4S,5R)-N-benzoyl-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid potassium salt (**6Ab**, Preparation No. 3, 91.4 mg, approximately 0.15 mM) in ethyl acetate is washed with 5% aqueous NaHSO_4 . The ethyl acetate solution is dried and evaporated leaving the corresponding acid **7Ab**. The residue is dissolved in methylene chloride
20 (0.8 ml) and toluene (1.75 ml), and combined with 7-triethylsilyl-baccatin III (68 mg). The mixture is treated with 4-dimethylaminopyridine (6.3 mg) and 1,3-dicyclohexylcarbodiimide (34 mg). The reaction is heated to 80°C for 90 minutes, cooled, filtered, and chromatographed on silica gel in ethyl acetate-hexane mixtures. An 86% yield of the coupled product **9AbA** was obtained.

- 25 NMR (CDCl_3 , TMS): δ 0.58 (m, 6H); 0.90 (m); 1.73 (s, 3H); 1.87 (m, 1H); 2.03 (m, 3H); 2.17 (bs, 3H); 2.20 (s, 3H); 2.23 (m, 2H); 2.50 (m, 1H); 3.78 (bs, 3H); 3.80 (s, 3H); 3.85 (d, 1H); 4.13 (d, 1H); 4.27 (d, 1H); 4.50 (m, 1H); 4.90 (m, 2H); 5.63 (bs, 1H); 5.68 (d, 1H); 6.25-6.48 (m, 3H); 6.50 (s, 1H); 6.86 (s, 1H); 7.09 (m, 1H); 7.15-7.65 (m, 13H); 8.05 (d, 2H).

Preparation No. 5: Preparation of Taxol (Compound **10AA**)

- 30 7-TES-baccatin III-13-(4S,5R)-N-Benzoyl-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (**9AbA**) is deprotected by stirring in 0.1 M HCl in methanol for 10 minutes. After diluting with ethyl acetate, the solution is washed with 5% NaHCO_3 , dried and evaporated. The product is purified by column chromatography on silica gel in acetone-hexane mixtures. The proton and carbon NMR data are identical with natural taxol.

Preparation No. 6: Preparation of (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (5Ba, & 5Bb)

N-Boc- β -phenyl isoserine methyl ester (3B) (0.5 g, 1.69 mM) is dissolved in dry THF (10 mL) and toluene (10 mL) and concentrated to dryness to remove any water of
5 crystallization. The residue is then dissolved in dry THF (10 mL) and the solution treated with 2,4-dimethoxy benzaldehyde dimethyl acetal (4) (0.425 g, 2.0 mM) and pyridinium p-toluenesulfonate (12 mg) and the solution warmed to reflux. After 30 minutes the reaction is cooled to RT and allowed to stand overnight. It is then again warmed to reflux for 3 hours. The reaction is checked by TLC and is found to be incomplete. The reaction is then heated to 85°C
10 to distill off about 2/3 of the THF. Then fresh THF (10 mL) and acetal (200 mg) is added and the reaction refluxed another 2 hours. TLC shows the reaction to be finished at this point. The reaction is concentrated in vacuo and the residue chromatographed over 100 g silica gel packed in (15-85) acetone-hexane. The column is eluted with acetone-hexane (500 mL of 15-85 and 500 mL of 20-80). Fractions of 20 mL are collected. The desired product isomers elute as a
15 mixture. The fractions containing the mixture of 5Ba & 5Bb and are combined and concentrated in vacuo leaving a white foam. The foam is rechromatographed over 100 g silica gel packed and eluted with (10-90) EtOAc-toluene. Fractions of 20 mL are collected and analyzed by TLC. There is thus isolated 34 mg of the less polar isomer 5Ba, 187 mg of a mixture of less polar and more polar isomers 5Ba and 5Bb, and 500 mg of the more polar
20 isomer 5Bb.

Isomer 5Bb is crystallized from EtOAc-hexane to give white crystals (378 mg).

The mixture of isomers is also crystallized from EtOAc-hexane to give crystalline 5Bb (113 mg) of similar purity by TLC as the mother liquors from the isomer 5Bb crystallization. These crystals and the mother liquors are therefore combined and recrystallized from
25 EtOAc-hexane to give more pure 5Bb (160 mg).

Data for 5Ba:

TLC: silica gel 60 ; 10% EtOAc-90% toluene; R_f : 0.44.

^1H NMR (CDCl_3 ; TMS): δ 1.26 (s, 9H); 3.80 (s, 3H); 3.84 (s, 3H); 3.85 (s, 3H); 4.86 (d, 1H); 5.24 (s, 1H); 6.40 (dd, 1H); 6.47 (d, 1H); 6.72 (s, 1H); 7.12 (d, 1H); 7.30-7.43 (m, 3H);
30 7.53 (d, 2H).

Data for 5Bb:

TLC: silica gel 60 ; 10% EtOAc-90% toluene; R_f : 0.38.

^1H NMR (CDCl_3 ; TMS): δ 1.10 (s, 9H); 3.52 (bd, 3H); 3.81 (s, 3H); 3.87 (s, 3H); 4.54 (d, 1H); 5.43 (bs, 1H); 6.48 (s, 2H); 6.81 (bs, 1H); 7.13 (bs, 1H); 7.30-7.48 (m, 5H).
35 UV: EtOH; 233 (10,600), 260sh (1010), 277 (2840), 281sh (2680).

Elemental analysis: Calculated: C 65.00; H 6.59; N 3.16.

Found: C 64.86; H 6.42; N 3.24.

Preparation No. 7: Preparation of (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (6Ba) and its free acid 7Ba

A 100 mg (0.23 mM) quantity (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (Preparation No. 6, 5Ba) is stirred at room temperature under nitrogen in 3 mL MeOH. Added 0.1 mL water and 43 mg (0.31 mM) potassium carbonate. After 1 hour, TLC shows no starting material left. Store in freezer overnight. The next morning the solvent is evaporated to give (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (6Ba). The residue is partitioned between methylene chloride and water containing 0.9 mL 1N HCl. The layers are separated and the aqueous layer reextracted with methylene chloride. The organic layers are combined, dried over sodium sulfate and evaporated. This leaves (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid (7Ba) as a white solid.

TLC (silica gel 60): 20% EtOAc-80% hexane-2% HOAc: Rf: 0.07

¹H NMR (CDCl₃; TMS): δ 1.26 (s, 9H); 3.76 (s, 6H); 4.77 (s, 1H); 5.34 (s, 1H); 6.33-6.45 (d, 2H); 6.60 (s, 1H); 7.07-7.16 (d, 1H); 7.24-7.40 (m, 3H); 7.42-7.54 (d, 2H).

Preparation No. 8: Preparation of 7-TES-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9BaA)

A 0.23 mM quantity (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid (Preparation No. 7, 7Ba) is dissolved in 1.5 mL methylene chloride-3 mL toluene. To this is added 106 mg (0.15 mM) 7-TES-baccatin III (8A), 11 mg (0.09 mM) DMAP and 49 mg (0.24 mM) DCC. The reaction is stirred under nitrogen and heated to 75°C for 90 minutes then cooled to RT. The resultant urea side product is removed by filtration and the filtrate is evaporated under vacuum. The residue is chromatographed over 20 g silica gel, eluting with 30-70 EtOAc-hexane. Fractions of 5 mL are collected, analyzing them by TLC. Fractions 17-34 contain the desired product and are combined and evaporated. 7-TES-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9BaA) is obtained as a white solid.

TLC: silica gel 60; 30% EtOAc-70% hexane; Rf: 0.56

Mass Spec (FAB, *m/z*) 1112, 1012, 874, 328, 284, 115, 105, 87.

¹H NMR (CDCl₃; TMS): δ 0.52-0.66 (m, 6H); 0.85-1.00 (m, 9H); 1.80-1.93 (m, 1H); 2.15 (s, 3H); 2.20 (s, 3H); 2.21-2.30 (m, 1H); 2.40-2.54 (m, 1H); 3.82 (s, 3H); 3.87 (s, 3H); 3.81 (d, 1H); 4.10 (d, 1H); 4.26 (d, 1H); 4.49 (m, 1H); 4.83-4.93 (m, 2H); 5.31 (d, 1H); 5.67 (d, 1H); 6.29 (t, 1H); 6.38-6.53 (m, 3H); 6.69 (s, 1H); 7.13 (d, 1H); 7.29-7.65 (m, 8H); 8.05 (d, 2H).

Preparation No. 9: Preparation of 13-(N-Boc- β -phenyl isoserinyl)-baccatin III (10BA)

A 0.1 M HCl solution is prepared from 0.071 mL acetyl chloride and 9.929 mL of MeOH, leaving it sit for 30 minutes before using.

To 57 mg (0.051 mM) 7-TES -baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-
5 4-phenyl-5-oxazolidinecarboxylic acid ester (Preparation No. 8, 9BaA) is added 0.5 mL of the above methanolic HCl solution with stirring under nitrogen. The reaction is complete after 75 minutes as shown by TLC. The reaction mixture is partitioned between ethyl acetate-5% sodium bicarbonate. The layers are separated and the aqueous layer reextracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated under
10 vacuum.

The crude product is chromatographed over 10 g silica gel, eluting with 50-50 ethyl acetate-toluene. Fractions of 2mL are collected, analyzing them by TLC. Pure product is found in fractions 19-42, which are combined and evaporated. 13-(N-Boc- β -phenyl isoserinyl)-baccatin III (10BA) is obtained as a white solid.

15 TLC: silica gel 60; 50-50 EtOAc-toluene; R_f: 0.38.

Mass Spec (FAB): (M+H) measured at 850.3680; theory for C₄₅H₅₆N₁O₁₅ is 850.3650; m/z 794, 569, 509, 105, 57.

¹H NMR (CDCl₃, TMS): δ 1.14 (s, 3H); 1.27 (s, 3H); 1.33 (s, 9H); 1.67 (s, 3H); 1.84 (s, 3H); 2.24 (s, 3H); 2.38 (s, 3H); 3.44 (d, 1H); 3.81 (d, 1H); 4.17 (d, 1H); 4.30 (d, 1H); 4.41
20 (m, 1H); 4.63 (bs, 1H); 4.95 (d, 1H); 5.26 (bd, 1H); 5.43 (bd, 1H); 5.67 (d, 1H); 6.23 (t, 1H); 6.28 (s, 1H); 7.27-7.45 (m, 5H); 7.50 (t, 2H); 7.62 (t, 1H); 8.11 (d, 2H).

Preparation No. 10: Preparation of (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid Potassium Salt (6Bb)

A solution of (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic
25 acid methyl ester (Preparation No. 6; 5Bb, 374 mg, 0.84 mM) in MeOH (11 mL) is stirred at RT under nitrogen and treated with water (0.37 mL) and potassium carbonate (161 mg, 1.17 mM). After 2 hours, TLC indicates the reaction to be about 70% done. After stirring overnight, the reaction is found to be complete. The solvent is evaporated and the residue dissolved in 10 mL water and freeze dried. This leaves 507 mg fluffy white solid, which contains (4S,5R)-N-
30 Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (6Bb, 393 mg).

TLC: silica gel; 20% EtOAc-80% hexane; R_f: origin.

Preparation No. 11: Preparation of 7-TES-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9BbA)

35 A 0.12 mM quantity of crude (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (Preparation No. 10, 6Bb) is partitioned between ethyl

acetate-5% sodium bisulfate. The layers are separated and the aqueous layer reextracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum.

The resulting acid 7Bb is dissolved in 0.8 mL methylene chloride-1.5 mL toluene along
5 with 53 mg (0.076 mM) of 7-TES-baccatin III (8A; See Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Vogelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917.), 6 mg (0.049 mM) 4-dimethylaminopyridine (DMAP) and 25 mg (0.12 mM) dicyclohexylcarbodiimide (DCC). The reaction is stirred under nitrogen and heated to 75°C for 90 minutes. The reaction is cooled to room temperature and the urea side product filtered off. The filtrate is evaporated
10 under vacuum.

The residue is chromatographed over 15 g silica gel, eluting with 30-70 EtOAc-hexane. Fractions of 7 mL are collected, analyzing them by TLC. Fractions 16-38 contain the product and are combined and evaporated. 7-TES-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9BbA) is obtained as a white
15 solid.

TLC: silica gel 60; 30% EtOAc-70% hexane; Rf: 0.33

Mass Spec (FAB, *m/z*) 1112, 1012, 384, 328, 284, 115, 105, 87, 57.

¹H NMR (CDCl₃; TMS): δ 0.50-0.61 (m, 6H); 0.84-0.97 (m, 9H); 1.08 (s, 9H); 2.21 (s, 3H); 3.67 (d, 1H); 3.80 (s, 3H); 3.90 (s, 3H); 4.07 (d, 1H); 4.23(d, 1H); 4.40 (m, 1H); 4.53 (bd, 1H); 4.87 (d, 1H); 5.44 (bd, 1H); 5.60 (d, 1H); 6.34 (s, 1H); 6.44 (bs, 1H); 6.48 (s, 1H); 7.20 (bs, 1H); 7.30-7.50 (m, 7H); 7.60 (t, 1H); 8.01 (d, 2H).
20

Preparation No. 12: Preparation of 13-(N-Boc-β-phenyl isoserinyl)-baccatin III (10BA)

A 0.1 M HCl solution is prepared from 0.071 mL acetyl chloride and 9.929 mL of MeOH, leaving it sit for 30 minutes before using.

To 45 mg (0.040 mM) 7-TES-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (Preparation No. 11, 9BbA) is added 0.395 mL of the above methanolic HCl solution with stirring under nitrogen. The reaction is complete after 20 minutes as shown by TLC.

After 30 minutes the reaction mixture is partitioned between ethyl acetate-5% sodium
30 bicarbonate. The layers are separated and aqueous layer reextracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum.

The crude product is chromatographed over 5 g silica gel, eluting with 50-50 ethyl acetate-toluene. Fractions of 5 mL are collected and analyzed by TLC. Pure product is found in fractions 5-12 which are combined and evaporated. 13-(N-Boc-β-phenyl isoserinyl)- baccatin
35 III (10BA) is obtained as a white solid.

TLC: silica gel 60; 50-50 EtOAc-toluene; Rf: 0.42

¹H NMR (CDCl₃, TMS): δ 1.15 (s, 3H); 1.27 (s, 3H); 1.33 (s, 9H); 1.68 (s, 3H); 1.85 (s, 3H); 2.25 (s, 3H); 2.38 (s, 3H); 3.44 (d, 1H); 3.80 (d, 1H); 4.17 (d, 1H); 4.30 (d, 1H); 4.41 (m, 1H); 4.62 (bs, 1H); 4.95 (d, 1H); 5.26 (bd, 1H); 5.43 (bd, 1H); 5.67 (d, 1H); 6.23 (t, 1H); 6.29 (s, 1H); 7.13-7.45 (m, 5H); 7.49 (t, 2H); 7.62 (t, 1H); 8.11 (d, 2H).

5 **Preparation No. 13:** Preparation of 7-(2,2,2-trichloroethoxycarbonyl)-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (**9BaB**, **9BbB**)

A 0.39 mM quantity of (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (**6Ba**, **6Bb**) is partitioned between ethyl acetate-5% sodium bisulfate. The layers are separated and the aqueous layer reextracted with ethyl acetate.

10 The organic layers are combined, dried over sodium sulfate and evaporated under vacuum.

The residual acid **7Ba**, **7Bb** is dissolved with stirring under nitrogen in 2 mL methylene chloride-6 mL toluene. To this is added 187 mg (0.245 mM) 7-(2,2,2-trichloroethoxycarbonyl)-baccatin III (**8B**, See for example Mangatal, L.; Adeline, M.-T.; Guenard, D.; Gueritte-Vogelein, F.; Potier, P. *Tetrahedron* 1989, 45, 4177.), followed by 22 mg (0.18 mM) DMAP and 80 mg

15 (0.39 mM) DCC. Soon after everything goes into solution, the urea side product starts to precipitate. The reaction is heated to 80°C for 70 minutes, following the reaction by TLC. After cooling to room temperature, the solid is filtered off and the filtrate evaporated under vacuum.

The crude product is chromatographed over 50 g silica gel, eluting with 400 mL 30-70, 200 mL 40-60, 100 mL 70-30 ethyl acetate-hexane. Fractions of 15 mL are collected, analyzing them by

20 TLC. The following fractions are combined and evaporated under vacuum to give white solids.

Fr 14-20, less polar isomer **9BaB**

Fr 21-26, mixed isomers **9BaB**, **9BbB**

Fr 27-32, more polar isomer **9BbB**

Fr 37-44, recovery of starting alcohol **8B**

25 Data for isomer **9BaB**:

TLC: silica gel 60; 40-60 ethyl acetate-hexane; R_f: 0.67.

¹H NMR (CDCl₃, TMS) δ 1.26 (s); 1.82 (s, 3H); 2.12 (s, 3H); 2.19 (s, 3H); 2.58 (m, 1H); 3.81 (s, 3H); 3.91 (s, 3H); 3.97 (d, 1H); 4.13 (d, 1H); 4.28 (d, 1H); 4.66 (d, 1H); 4.92 (m, 2H); 5.03 (d, 1H); 5.36 (d, 1H); 5.63 (m, 1H); 5.67 (d, 1H); 6.32 (m, 1H); 6.40 (s, 1H); 6.51 (d, 1H); 6.69 (s, 1H); 7.16 (d, 1H); 7.37-7.62 (m, 8H); 8.02 (d, 2H).

Data for isomer **9BbB**:

TLC: silica gel 60; 40-60 ethyl acetate-hexane; R_f: 0.55.

¹H NMR (CDCl₃, TMS) δ 2.17 (bs); 3.47 (m); 3.79-3.94 (m); 4.08 (d); 4.27 (d); 4.54 (m); 4.65 (m); 4.89 (d); 5.01 (m); 5.40 (m); 5.50 (m); 5.62 (d); 6.24 (bs); 6.49 (bs); 7.37-7.65 (m); 8.03 (d).

Preparation No. 14: Preparation of 7-(2,2,2-trichloroethoxycarbonyl)-13-(N-Boc- β -phenyl isoserinyl)-baccatin III **10BB**

A 0.1M HCl solution in MeOH is prepared from 0.071 mL acetyl chloride and 9.929 mL MeOH and left standing for 30 minutes before using.

5 A 252 mg (0.216 mM) quantity of 7-(2,2,2-trichloroethoxycarbonyl)-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (Preparation No. 13; **9BaB,9BbB**) is stirred at RT under nitrogen with 2.2 mL of the above 0.1 M HCl solution in MeOH. The reaction is followed by TLC and since it is incomplete after 20 minutes, another 0.5 mL HCl solution is added and the reaction continued for 15 minutes.

10 The reaction mixture is then diluted with ethyl acetate and washed with 5% sodium bicarbonate. The layers are separated and the aqueous layer reextracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum. The crude product is chromatographed over 30 g silica gel, eluting with 200 mL 35-65 and 300 mL 40-60 ethyl acetate-hexane. Fractions of 5 mL are collected, analyzing them by TLC. Fractions
15 25-54 contain the pure product and are combined and evaporated under vacuum to give 7-(2,2,2-trichloroethoxycarbonyl)-13-(N-Boc- β -phenyl isoserinyl)-baccatin III **10BB**, as a white solid.

TLC: silica gel 60; 40-60 ethyl acetate-hexane; Rf: 0.36

Mass Spec (FAB, m/z) ($M+H$) at 1024, 1026, 1028; ($M+H$) measured at 1024.2656; theory for $C_{48}H_{57}Cl_3N_1O_{17}$ is 1024.2692; 1024, 968, 924, 743, 683, 105, 57.

20 1H NMR (CDCl₃, TMS) δ 1.17 (s, 3H); 1.24 (s, 3H); 1.34 (s, 9H); 1.83 (s, 3H); 1.91 (s, 3H); 2.17 (s, 3H); 2.39 (s, 3H); 2.62 (m, 1H); 3.60 (d, 1H); 3.94 (d, 1H); 4.16 (d, 1H); 4.30 (d, 1H); 4.63 and 5.04 (2d, 2H); 4.62 (bs, 1H); 4.95 (d, 1H); 5.26 (bd, 1H); 5.45-5.60 (m, 2H); 5.66 (d, 1H); 6.20 (t, 1H); 6.36 (s, 1H); 7.24-7.44 (m, 5H); 7.49 (t, 2H); 7.61 (t, 1H); 8.08 (d, 2H).

25 **Preparation No. 15:** Preparation of 13-(N-Boc- β -phenyl isoserinyl)-baccatin III (**10BA**) and 7-(2,2-dichloroethoxycarbonyl)-13-(N-Boc- β -phenyl isoserinyl)-baccatin III **10BG**.

A 150 mg (0.146 mM) quantity of 7-(2,2,2-trichloroethoxycarbonyl)-13-(N-Boc- β -phenyl isoserinyl)-baccatin III (Preparation No. 14, **10BB**) is stirred at RT under nitrogen in 13.5 mL MeOH and 1.5 mL HOAc. To this is added 150 mg activated zinc and the reaction heated to
30 50°C for 60 minutes. The reaction is followed by TLC and adding 4 more 150 mg portions of zinc, heating for 45 minutes after each addition. The reaction mixture is filtered and the filtrate evaporated under vacuum. The residue is partitioned between methylene chloride-water. The layers are separated and the aqueous layer backextracted with methylene chloride. The organic layers are combined, dried over sodium sulfate and evaporated.

35 The crude product is chromatographed over 20 g silica gel, eluting with 200 mL 60-40 and 200 mL of 70-30 ethyl acetate-hexane. Fractions of 5 mL are collected, analyzing them by

TLC. The following fractions are combined and evaporated to give white solids.

Fr 9-13, 7-(2,2-dichloroethoxycarbonyl)-13-(N-Boc- β -phenyl isoserinyl)-baccatin III 10BG.

Fr 14-44, 13-(N-Boc- β -phenyl isoserinyl)-baccatin III (10BA)

5 Data for 7-(2,2-dichloroethoxycarbonyl)-13-(N-Boc- β -phenyl isoserinyl)-baccatin III 10BG

TLC: silica gel 60; 50-50 ethyl acetate-hexane; Rf: 0.81 (this product and starting material run together in this TLC system).

¹H NMR: (CDCl₃, TMS) δ 1.17 (s, 3H); 1.24 (s, 3H); 1.35 (s, 9H); 1.61 (s, 3H); 1.81 (s, 3H); 2.19 (s, 3H); 2.39 (s, 3H); 2.52-2.68 (m, 1H); 3.37 (d, 1H); 3.92 (d, 1H); 4.16 (d, 1H); 10 4.32 (d, 1H); 4.53 (m, 2H); 4.63 (bs, 1H); 4.95 (d, 1H); 5.26 (bd, 1H); 5.40 (bd, 1H); 4.48 (m, 1H); 5.67 (d, 1H); 5.96 (m, 1H); 6.20 (t, 1H); 6.45 (s, 1H); 7.28-7.44 (m, 5H); 7.50 (t, 2H); 7.62 (t, 1H); 8.10 (d, 2H).

Data for 10BA:

TLC: silica gel 60; 50-50 ethyl acetate-hexane; Rf: 0.32

15 ¹H NMR: (CDCl₃, TMS) δ 1.14 (s, 3H); 1.24 (s, 3H); 1.32 (s, 9H); 1.67 (s, 3H); 1.84 (s, 3H); 2.23 (s, 3H); 2.37 (s, 3H); 2.44-2.59 (m, 1H); 2.64 (bd, 1H); 3.70 (bs, 1H); 3.78 (d, 1H); 4.15 (d, 1H); 4.28 (d, 1H); 4.40 (m, 1H); 4.61 (bs, 1H); 4.94 (d, 1H); 5.25 (bd, 1H); 5.57 (bd, 1H); 5.65 (d, 1H); 6.22 (t, 1H); 6.29 (s, 1H); 7.24-7.44 (m, 5H); 7.48 (t, 2H); 7.60 (t, 1H); 8.08 (d, 2H).

20 Preparation No. 16: Preparation of 7,10-bis-Troc-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9BbC)

Crude (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (Preparation No. 10; 6Bb) (0.089 mM) is partitioned between EtOAc- 5% NaHSO₄. The layers are separated and the aqueous layer reextracted with EtOAc. The organic 25 layers are combined, dried over sodium sulfate and evaporated under vacuum leaving (4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid (7Bb). This residue is stirred at room temperature under nitrogen in methylene chloride (0.8 mL) and toluene (1.5 mL). To this is added 7,10-bis-Troc-10-deacetyl baccatin III (8C, see for example Senilh, V.; Gueritte-Vogelein, F.; Guenard, D.; Colin, M.; Potier, P. C. R. Acad. Sci. Paris 1984, 299, 30 4177.), 50 mg, 0.056 mM. The resultant solution is treated with 4-dimethylaminopyridine (5 mg, 0.04 mM) and 1,3-dicyclohexyl carbodiimide (18 mg, 0.087 mM) and then heated to 75°C (25 min). TLC analysis after 15 minutes heating shows the reaction to be complete.

The precipitated dicyclohexyl urea is filtered off. The filtrate is coated on silica gel (1 g) and chromatographed over silica gel (10 g), which is eluted with EtOAc-hexane (30-70) .

35 Fractions of 4 mL are collected, analyzing them by TLC. Fractions 16-42 contain the product

and are combined and evaporated under vacuum. This produces 7,10-bis-Troc-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9BbC) as a white solid.

TLC (silica gel 60): 40% EtOAc-60% hexane; R_f : 0.56

5 Mass Spec (FAB, m/z) 1304, 1306, 1308 (M+H), 1204, 875, 683, 384, 328 284, 105 (base), 57.

^1H NMR (CDCl_3 ; TMS): δ 1.07 (s, 3H); 1.14 (s, 3H); 1.22 (s, 3H); 1.79 (s, 3H); 2.56 (m, 1H); 3.79 (d, 1H); 3.81 (s, 3H); 3.89 (s, 3H); 4.08 (d, 1H); 4.25 (d, 1H); 4.54 (d, 1H); 4.59 and 4.88 (2d, 2H); 4.78 (s, 2H); 4.89 (bt, 1H); 5.43(m, 1H); 5.50 (m, 1H); 5.62 (d, 1H); 6.05 (bs, 1H); 6.12 (s, 1H); 6.47 (d, 1H); 6.49 (s, 1H); 6.75 (bs, 1H); 7.21. (m, 1H); 7.35-7.53 (m, 7H); 7.62 (t, 1H); 8.01 (d, 2H).

Preparation No. 17: Preparation of 7,10-bis-Troc-13-(N-Boc- β -phenyl isoserinyl)-baccatin III (10BC).

Acetyl chloride (0.071 mL, 80 mg, 1.0 mM) is added to methanol (10 mL) and the solution allowed to stand for 30 minutes, giving a 0.1 N HCl solution. 7,10-Bis-Troc-baccatin III-13-(4S,5R)-N-Boc-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (Preparation No. 16; 9BbC) (73 mg, 0.056 mM) is dissolved in the above methanolic HCl solution (0.553 mL) and allowed to stand (25 min). The reaction is then diluted with EtOAc and washed with 5% sodium bicarbonate. The layers are separated and the aqueous layer reextracted with EtOAc. The organic phases are combined, dried over sodium sulfate and evaporated under vacuum. The crude product is coated on silica gel (1 g) and chromatographed over silica gel (10 g). The column is eluted with 20% EtOAc-80% toluene. Fractions of 4 ml are collected, analyzing them by TLC. Pure product is found in fractions 10-20 which are combined and evaporated. Impure product in fractions 7-9, is rechromatographed as above. Fractions 11-26 contained the pure product and are combined with pure product from the first column. This gives 7,10-bis-Troc-13-(N-Boc- β -phenyl isoserinyl)-baccatin III (10BC) as a white solid.

TLC (silica gel 60): 30% EtOAc-70% toluene; R_f : 0.59; the side product 2,4-dimethoxy benzaldehyde runs just ahead of product and right where starting material comes.

Mass Spec (FAB, m/z) 1156, 1158, 1160 (M+H), 1100, 1056, 701, 685, 105 (base), 57.

30 ^1H NMR (CDCl_3 ; TMS): δ 1.20 (s, 3H); 1.27 (s, 3H); 1.35 (s, 9H); 1.85(s, 3H); 1.95 (s, 3H); 2.35 (s, 3H); 3.41 (d, 1H); 3.90 (d, 1H); 4.17 (d, 1H); 4.33 (d, 1H); 4.60 and 4.92 (2d, 2H); 4.62 (bs, 1H); 4.78 (s, 2H); 4.95 (d, 1H); 5.26 (bd, 1H); 5.42 (bd, 1H); 5.54 (dd, 1H); 5.69 (d, 1H); 6.21 (t, 1H); 6.24 (s, 1H); 7.12-7.42 (m, 6H); 7.49 (t, 2H); 7.62 (t, 1H); 8.09 (d, 2H).

Preparation No. 18: Preparation of 7-(2,2-dichloroethoxycarbonyl)-13-(N-Boc- β -phenyl isoserinyl)-baccatin III (10BD), 10-(2,2-dichloroethoxycarbonyl)-13-(N-Boc- β -phenyl isoserinyl)-baccatin III (10BE), and 13-(N-Boc- β -phenyl isoserinyl)-baccatin III (10BF, Taxotere)

7,10-Bis-Troc-13-(N-Boc- β -phenyl isoserinyl)-baccatin III (Preparation No. 17; **10BC**) (48 mg, 0.041mM) is stirred at room temperature under nitrogen in 90% MeOH-10% HOAc (3 mL) and the solution treated with activated zinc (85 mg). After 30 minutes reaction a cloudiness occurs. One mL more of the MeOH-HOAc solution is added and the reaction becomes clear. TLC after 30 and 60 minutes look very similar, namely no starting material and two minor and one major more polar products. After 70 minutes reaction, the solid zinc is filtered off. The filtrate is evaporated under vacuum. The residue is partitioned between methylene chloride and water. The layers are separated and the aqueous layer re-extracted with methylene chloride. The organic layers are again washed with water, dried over sodium sulfate, combined and evaporated under vacuum. The crude product mixture is coated on silica gel (1 g) and chromatographed over silica gel (5 g). The column is eluted with EtOAc-hexane (100 mL each of 40-60, 50-50, 60-40, and 70-30). Fractions of 4 mL are collected, analyzing them by TLC. The following fractions are combined and evaporated.

Fr. 12-24, **10BD**

Fr. 29-42, **10BE**

Fr. 48-84, **10BF**

Data for **10BD**:

TLC (silica gel 60): 60% EtOAc-40% hexane; R_f : 0.92

Mass Spec (FAB, m/z) 948, 950, 952 (M+H), 892, 848, 830, 667, 649, 105 (base), 57.

^1H NMR (CDCl_3 ; TMS): δ 1.09 (s, 3H); 1.23 (s, 3H); 1.34 (s, 9H); 1.86(s, 3H); 1.89 (s, 3H); 2.04 (m, 1H); 2.29 (d, 2H); 2.39 (s, 3H); 3.4 (bs, 1H); 3.99 (d, 1H); 4.05 (s, 1H); 4.20 (d, 1H); 4.33 (d, 1H); 4.48 (m, 2H); 4.62 and 4.93 (2d, 2H); 5.30 (m, 1H); 5.37 (s, 1H); 5.46 (d, 1H); 5.68 (d, 1H); 5.83 (t, 1H); 6.21 (t, 1H); 7.3-7.45 (m, 6H); 7.50 (t, 2H); 7.62 (t, 1H); 8.10 (d, 2H).

Data for **10BE**:

TLC (silica gel 60): 60% EtOAc-40% hexane; R_f : 0.65.

Mass Spec (FAB, m/z) 948, 950, 952 (M+H), 892, 848, 667, 527, 509, 105 (base), 57.

^1H NMR (CDCl_3 ; TMS): δ 1.16 (s, 3H); 1.27 (s, 3H); 1.33 (s, 9H); 1.70 (s, 3H); 1.89 (s, 3H); 2.39 (s, 3H); 2.57 (m, 1H); 3.40 (d, 1H); 3.75 (d, 1H); 4.17 (d, 1H); 4.33 (d, 1H); 4.35 (m, 1H); 4.56 (dd, 2H); 4.64 (m, 1H); 4.95 (d, 1H); 5.28 (m, 1H); 5.37 (d, 1H); 5.68 (d, 1H); 5.92 (d, 1H); 6.15 (s, 1H); 6.25 (t, 1H); 7.20-7.45 (m, 6H); 7.50 (t, 2H); 7.64 (t, 1H); 8.10 (d, 2H).

Data for **10BF**:

TLC (silica gel 60): 60% EtOAc-40% hexane; R_f : 0.23.

Mass Spec (FAB, m/z) 808 (M+H), 790, 752, 708, 527, 509, 345, 327, 105 (base), 57.

^1H NMR (CDCl_3 ; TMS): δ 1.12 (s, 3H); 1.23 (s, 3H); 1.33 (s, 9H); 1.74 (s, 3H); 1.84

(s, 3H); 2.37 (s, 3H); 2.56 (m, 1H); 3.60 (bs, 1H); 3.89 (d, 1H); 4.18 (d, 1H); 4.21 (m, 1H); 4.30 (d, 1H); 4.32 (s, 1H); 4.62 (bs, 1H); 4.94 (d, 1H); 5.23 (s, 1H); 5.28 (bs, 1H); 5.54 (d, 1H); 5.66 (d, 1H); 6.20 (t, 1H); 7.25-7.45 (m, 6H); 7.50 (t, 2H); 7.61 (t, 1H); 8.09 (d, 2H).

Preparation No. 19: Preparation of (2R,3S)-N-carbobenzyloxy- β -phenyl isoserine methyl ester (3C)

A solution of (2R,3S)- β -phenyl isoserine methyl ester (2) (Preparation No. 1, 2 mM) in pyridine containing a small amount of DMAP is cooled in an ice bath and treated with benzyl chloroformate (0.8 ml). After stirring at room temperature overnight, the reaction is diluted with ethyl acetate, washed with 5% aqueous sodium bisulfate, dried and evaporated. The product is obtained pure by silica gel chromatography in ethyl acetate-hexane mixtures. Mp 120-121°C. NMR(CDCl₃, TMS): δ 3.26 (m, 1H); 3.79 (s, 3H); 4.47 (m, 1H); 5.06 (m, 2H); 5.27 (d, 1H); 5.75 (m, 1H); 7.20-7.50 (m, 10 H).

Preparation No. 20: Preparation of (4S,5R)-N-Carbobenzyloxy-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester 5Cb

N-Carbobenzyloxy- β -phenyl isoserine methyl ester (Preparation No. 19, 3C, 0.375 g, 1.14 mM) is dissolved in dry THF (10 mL) and the solution treated with 2,4-dimethoxy benzaldehyde dimethyl acetal (4, 0.300 g, 1.42 mM) and pyridinium p-toluenesulfonate (10 mg) and the solution heated to distill off the THF and methanol. After 1/2 the THF is distilled off, THF (10 mL) is added and the reaction distilled to 1/2 volume again. The process is repeated three times. The reaction is then concentrated in vacuo and the residue chromatographed over 75 g silica gel packed and eluted in acetone-hexane (300 mL of 20-80 and 300 mL of 25-75). Fractions of 20 mL are collected and analyzed by TLC. The following fractions are combined and evaporated under vacuum.

Fr. 26-44, 543 mg, isomer 5Cb (other runs have shown this to be the more polar isomer).

Data for 5Cb:

TLC: silica gel; 20% acetone-80% hexane; R_f: 0.19.

¹H NMR (CDCl₃, TMS): δ 3.51 (bs, 3H); 3.81 (bs, 6H); 4.56 (d, 1H); 4.8 (bd, 1H); 4.94 (d, 1H); 5.54 (d, 1H); 6.4 (bs, 2H); 6.78 (d, 3H); 7.05-7.50 (m, 9H).

Preparation No. 21: Preparation of (4S,5R)-N-CBZ-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid potassium salt. 6Cb

(4S,5R)-N-CBZ-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid methyl ester (Preparation No. 20, 5Cb, 444 mg, 0.93 mM) is dissolved in 10 mL methanol. To the solution is added water (400 μ l) and potassium carbonate (200 mg, 1.45 mM). After stirring overnight no solids remain and TLC indicates very little methyl ester remaining. The solvent is concentrated in vacuo and water (20 ml) added to the oil. The solution is freeze dried leaving

638 mg fluffy white powder which contains 466 mg of the potassium salt 6Cb.

TLC: silica gel 60; 1:4 EtOAc:Toluene; R_f : origin.

Preparation No. 22: Preparation of 7-Triethylsilyl-Baccatin III-13-(4S,5R)-N-CBZ-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester. 9CbA

5 Crude (4S,5R)-N-CBZ-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid potassium salt (6Cb, Preparation No. 21; 75 mg, 0.11 mM) is partitioned between CH_2Cl_2 and 5% NaHSO_4 solution. The layers are separated and the aqueous layer extracted with EtOAc. The combined organic layers are filtered through anhydrous sodium sulfate and concentrated in vacuo leaving 51 mg of (4S,5R)-N-CBZ-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine-
10 carboxylic acid (7Cb).

7-Triethylsilyl-baccatin III (8A, 50 mg, 0.07 mM) is dissolved in 700 μL toluene. All of the (4S,5R)-N-CBZ-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid is added in a solution of CH_2Cl_2 . To the solution is added DCC (25 mg, 0.11 mM) and DMAP (4mg, 0.04 mM) and the solution heated to 80°C driving off the CH_2Cl_2 . The reaction is checked by
15 TLC and after 1.5 hours very little 7-triethylsilyl-baccatin III is seen. The reaction is allowed to cool and the slurry filtered. The filtrate is concentrated in vacuo and chromatographed over 7 gm of silica gel packed in 1:3 EtOAc:Hexane. The column is eluted with 40 mL 1:3 EtOAc:Hexane and 75 ml 1:2 EtOAc:Hexane collecting 3 ml fractions. The desired product is found in fractions 17-32.

20 Mass Spec (FAB-High Res.) Theory: 1146.4882 Found: 1146.4915

^1H NMR (CDCl_3 ; TMS): δ 0.51-0.59 (m,6H); 0.88-0.94 (m); 1.13 (s,3H); 1.18 (s,3H); 1.79-1.89 (m,1H); 2.17 (s,3H); 2.40-2.50 (m,1H); 3.67 (d,1H); 3.80 (br s,6H); 4.07 (d,1H); 4.22 (d,1H); 4.39 (m,1H); 4.54 (d,1H); 4.77 (d,1H); 4.86 (d,1H); 4.94 (d,1H); 5.54 (d,1H); 5.61 (d,1H); 5.90 (m,1H); 6.33 (s,1H); 6.43 (m,2H); 6.78 (m,3H); 7.12-7.21 (m,4H); 7.38-7.50
25 (m,7H); 7.59 (m,1H); 8.01 (d,2H)

Preparation No. 23: Preparation of 13-(N-CBZ- β -phenyl-isoserinyl)-baccatin III 10CA and 10-deacetyl-13-(N-CBZ- β -phenyl-isoserinyl)-baccatin III 10CB

7-Triethylsilyl-Baccatin III-13-(4S,5R)-N-CBZ-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9CbA, Preparation No. 22; 630 mg, 0.55 mM) is dissolved in
30 10 mL 0.1N HCl in methanol. The 0.1N HCl solution is made by diluting 71 μL acetyl chloride to 10 mL with methanol and allowing to react for a minimum of 0.5 hours. The reaction is checked by TLC and after 0.5 hours no starting materials is seen. The reaction solution is partitioned between brine, 5% NaHCO_3 solution, and EtOAc. The layers are separated and the organic layer is extracted with 5% NaHCO_3 solution. The combined aqueous
35 layers are extracted with EtOAc and the combined organic layers are filtered through anhydrous sodium sulfate. The solvent is concentrated in vacuo and the residue chromatographed over

60 gm silica gel packed in 1:1 EtOAc:Hexane. The column is eluted with 500 mL 1:1 EtOAc:Hexane, 250 mL 3:2 EtOAc:Hexane, 240 mL 2:1 EtOAc:Hexane collecting 25 mL fractions.

Fractions 16-36, 13-(N-CBZ- β -phenyl-isoserinyl)-baccatin III, 10CA

5 Fractions 44-52, 10-deacetyl-13-(N-CBZ- β -phenyl-isoserinyl)-baccatin III 10CB

Data for 10CA:

Mass Spec (FAB-High Res.) Theory: 884.3493 Found: 884.3490

¹H NMR (CDCl₃; TMS): δ 1.13 (s,3H); 1.80(s,3H); 1.86 (m,1H); 2.24 (s,3H); 2.37 (s,3H); 2.54 (m,2H); 3.43 (m,1H); 3.76(d,1H); 4.19 (d,1H); 4.28 (d,1H); 4.39 (m,1H); 4.66 (br s,1H); 4.90-4.97 (m,1H); 4.94 (d,1H); 5.05 (d,1H); 5.34 (d,1H); 5.64 (d,1H); 5.75 (d,1H); 10 6.23 (m,1H); 6.25 (s,1H); 7.17 (br s,2H); 7.25 (br s,3H); 7.29-7.41 (m,5H); 7.50 (m,2H); 7.61 (m,1H); 8.12 (d,2H)

Data for 10CB:

Mass Spec (FAB-High Res.) Theory: 842.3388 Found: 842.3364

15 ¹H NMR (CDCl₃; TMS): δ 2.37 (s,3H); 2.57 (m,1H); 3.40 (d,1H); 3.87 (d,1H); 4.18-4.32 (m); 4.65 (br s,1H); 4.92 (d,1H); 4.95 (d,1H); 5.06 (d,1H); 5.18 (s,1H); 5.35 (d,1H); 5.65 (d,1H); 5.78 (d,1H); 6.20 (m,1H); 7.18 (m,1H); 7.22-7.46 (m); 7.50 (m,2H); 7.61 (m,1H); 8.11 (d,2H)

Preparation No. 24: Preparation of 13-(β -phenyl isoserinyl)-baccatin III (11A) from

20 13-(N-Cbz- β -phenyl isoserinyl)-baccatin III (10CA)

A 405 mg (0.46 mM) quantity 13-(N-Cbz- β -phenyl isoserinyl)-baccatin III (Preparation No. 23; 10CA) is stirred at room temperature and hydrogenated at atmospheric pressure with 40 mL absolute ethanol and 100 mg 10% Pd/C. The reaction is followed by TLC, being complete after 5 hours.

25 The reaction is filtered through Celite, washing with ethyl acetate. The combined filtrate and wash are evaporated under vacuum. The residue is treated with a small amount of ethyl acetate and a larger amount of hexane and reevaporated twice more. 13-(β -phenyl isoserinyl)-baccatin III (11A) is obtained as a white solid.

TLC: silica gel 60; 70-30 EtOAc-hexane; Rf: streak between origin and 1/3 up the plate.

30 ¹H NMR (CDCl₃, TMS): δ 1.13 (s, 3H); 1.24 (s, 3H); 1.66 (s, 3H); 1.88 (s, 3H); 2.23 (s, 3H); 2.24 (s, 3H); 2.45-2.61 (m, 1H); 3.75 (d, 1H); 4.14 (d, 1H); 4.23-4.33 (m, 3 H); 4.40 (m, 1H); 4.93 (d, 1H); 5.63 (d, 1H); 6.13 (t, 1H); 6.27 (s, 1H); 7.26 (m, 1H); 7.39 (d, 4H); 7.52 (t, 2H); 7.65 (t, 1H); 8.06 (d, 2H).

Preparation No. 25: Preparation of (2R,3S)-N-(2,2,2-trichloroethoxycarbonyl)- β -phenyl isoserine

35 methyl ester (3D)

Following the general procedure of Preparation No. 19 [(2R,3S)-N-Carbobenzyloxy- β -

phenyl isoserine methyl ester (3C)], but starting with 2,2,2-trichloroethoxycarbonyl chloride to acylate the amine β -phenyl isoserine methyl ester (2) the product N-(2,2,2-trichloroethoxycarbonyl)- β -phenyl isoserine methyl ester (3D) is prepared.

Preparation No. 26: Preparation of (4S,5R)-N-(2,2,2-trichloroethoxycarbonyl)-2-(2,4-

5 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester 5Da & 5Db

Following the general procedure of Procedure 20 [Preparation of (4S,5R)-N-Carbobenzyloxy-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (5Cb)], but starting with (2,2,2-trichloroethoxycarbonyl)- β -phenyl isoserine methyl ester (3D) the product (4S,5R)-N-(2,2,2-trichloroethoxycarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (5Da, 5Db) is prepared.

Preparation No. 27: Preparation of (4S,5R)-N-(2,2,2-trichloroethoxycarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (6Da, 6Db)

Following the general procedure of Preparation 21 [(4S,5R)-N-Carbobenzyloxy-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (6Cb)], but starting with (4S,5R)-N-(2,2,2-trichloroethoxycarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (5Da, 5Db) the product (4S,5R)-N-(2,2,2-trichloroethoxycarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (6Da, 6Db) is prepared.

Preparation No. 28: Preparation of 7-Triethylsilyl-Baccatin III-13-(4S,5R)-N-(2,2,2-trichloroethoxycarbonyl)-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9DaA, 9DbA)

Following the general procedure of Preparation No. 22 [preparation of 7-Triethylsilyl-Baccatin III-13-(4S,5R)-N-CBZ-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester; 9CbA], but starting with (4S,5R)-N-(2,2,2-trichloroethoxycarbonyl)-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidine carboxylic acid (6Da, 6Db) is prepared the desired 7-Triethylsilyl-Baccatin III-13-(4S,5R)-N-(2,2,2-trichloroethoxycarbonyl)-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9DaA, 9DbA).

Preparation No. 29: Preparation of 13-(N-(2,2,2-trichloro-ethoxycarbonyl)- β -phenyl-isoserinyl)-baccatin III (10DA)

Following the general procedure of Preparation No. 23 [preparation of 13-(N-CBZ- β -phenyl-isoserinyl)-baccatin III (10CA)], but starting instead with 7-triethylsilyl-baccatin III-13-(4S,5R)-N-(2,2,2-trichloroethoxycarbonyl)-2-(2,4 dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9Da, 9Db)] the product 3-(N-(2,2,2-trichloroethoxycarbonyl)- β -phenyl-isoserinyl)-baccatin III (10DA) is prepared.

Preparation No. 30: Preparation of 13-(β -phenyl-isoserinyl)-baccatin III (11A) from 13-(N-(2,2,2-trichloro-ethoxycarbonyl)- β -phenyl-isoserinyl)-baccatin III (10DA)

13-(N-(2,2,2-trichloro-ethoxycarbonyl)- β -phenyl-isoserinyl)-baccatin III (Preparation No. 29; 10DA, 1g) is dissolved in methanol (50 mL) and the solution treated with zinc powder (2 g) and ammonium chloride (2g) with stirring at room temperature. After stirring 3 hr, the reaction is filtered and the filtrate evaporated under vacuum (less than 20 torr). The residue is partitioned between ethyl acetate and 5% aqueous sodium bicarbonate. The organic layer is separated, dried (sodium sulfate) and concentrated under vacuum leaving the product 13-(β -phenyl-isoserinyl)-baccatin III (11A).

10 Preparation No. 31: Preparation of 13-(N-Boc- β -phenyl isoserinyl)- baccatin III (10BA)

A 68 mg (0.09 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) is stirred at room temperature under nitrogen in 0.5 mL dry THF. To this is added 20 mg (0.092 mM) di-t-butyl-dicarbonate in 0.2 mL dry THF and 0.013 mL (0.093 mM) triethylamine. The reaction is allowed to react for 24 hours; TLC after 5 hours shows the reaction to be mostly done.

The reaction mixture is partitioned between ethyl acetate-brine. The layers are separated and the aqueous layer reextracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum.

The crude product is chromatographed over 10 g silica gel, eluting with 60-40 ethyl acetate-hexane. Fractions of 2 mL are collected, analyzing them by TLC. Fractions 12-30 contain the product and are combined and evaporated under vacuum. This produces the title compound, 10BA, as a white solid.

TLC: silica gel 60; 60-40 EtOAc-hexane; Rf: 0.46.

^1H NMR (CDCl_3 , TMS) δ 1.15 (s, 3H); 1.33 (s, 9H); 1.85 (s, 3H); 2.25 (s, 3H); 2.30 (m); 2.38 (s, 3H); 2.54 (m); 3.46 (d, 1H); 3.80 (d, 1H); 4.17 (d, 1H); 4.31 (d, 1H); 4.41 (m, 1H); 4.63 (bs, 1H); 4.95 (d, 1H); 5.28 (bd, 1H); 5.42 (bd, 1H); 5.67 (d, 1H); 6.24 (t, 1H); 6.29 (s, 1H); 7.18 (d, 1H); 7.38 (m, 5H); 7.50 (t, 2H); 7.62 (t, 1H); 8.10 (d, 2H).

Preparation No. 32: Preparation of 13-(N-(1-adamantoyl)- β -phenyl isoserinyl)-baccatin III (10EA)

30 A 44 mg (0.06 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) is stirred at 0°C under nitrogen in 1 mL dry pyridine. To this is added 0.2 ml methylene chloride containing 13 mg (0.06 mM) 1-adamantane-carbonyl chloride. After 30 minutes reaction, TLC shows the reaction to be complete.

The reaction is partitioned between 1N HCl-ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate and evaporated under vacuum.

The residue is chromatographed over 5 g silica gel, eluting with 65-35 EtOAc-hexane.

Fractions of 2 mL are collected, analyzing them by TLC. The product is found in fractions 8-23, which upon combining and evaporating leave 33 mg (60% yield) white solid. Spectral data still showed the presence of 1-adamantane carboxylic acid.

The impure product is dissolved in 1 mL freshly distilled THF. Excess ethereal
5 diazomethane is added and the reaction left to react for 30 minutes. The reaction is then evaporated under vacuum and chromatographed as before. Pure product is found in fractions 6-25, which upon evaporation leave 13-(N-(1-adamantoyl)- β -phenyl isoserinyl)-baccatin III 10EA, as a solid.

TLC: silica gel 60; 50-50 EtOAc-hexane; Rf: 0.48.

10 Mass Spec (FAB, m/z): (M+H) measured at 912.4168; theory for $C_{51}H_{62}N_1O_{14}$ is 912.4170; 912, 852, 834, 569, 551, 509, 344, 326, 298, 268, 180, 135, 105.

1H NMR ($CDCl_3$, TMS) δ 1.16 (s); 1.27 (s); 1.60-2.10 (m); 2.24 (s, 3H); 2.30 (m); 2.36 (s, 3H); 2.52 (m); 3.54 (d, 1H); 3.77 (d, 1H); 4.18 (d, 1H); 4.29 (d, 1H); 4.40 (m, 1H); 4.68 (m, 1H); 4.94 (d, 1H); 5.56 (dd, 1H); 5.68 (d, 1H); 6.15 (t, 1H); 6.28 (s, 1H); 6.47 (d, 1H); 7.37
15 (m, 5H); 7.50 (t, 2H); 7.61 (t, 1H); 8.10 (d, 2H).

Preparation No. 33: Preparation of 13-(N-(3-tetrahydrofuranyloxycarbonyl)- β -phenyl isoserinyl)-baccatin III (10FA)

13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) 16.8 mg, 0.022 mM) is treated with racemic 3-tetrahydrofuranol succinimidyl carbonate (5.0 mg, 0.023 mM), pyridine
20 (5 μ L), and methylene chloride (180 μ L). The reaction is stirred at room temperature 2 days. It is diluted with ethyl acetate and washed with 5% aqueous sodium bisulfate and 5% aqueous sodium bicarbonate. The organic solution was dried and evaporated to give a mixture of diastereomers, 13-(N-(3-tetrahydrofuranyloxycarbonyl)- β -phenyl isoserinyl)-baccatin III (10FA).

TLC: silica gel 60; 40-60 acetone hexane; Rf: 0.16.

25 1H NMR ($CDCl_3$, TMS) δ 1.16 (s); 1.27 (s); 1.68 (s+m); 1.83 (s); 1.90 (m); 2.25 (s+m); 2.37 (s); 2.55 (m); 3.7-4.0 (m); 4.18 (d, 1H); 4.30 (d, 1H); 4.43 (m, 1H); 4.64 (m, 1H); 4.95 (dd, 1H); 5.09 (m, 1H); 5.30 (m, 1H); 5.67 (m, 2H); 6.28 (s+m, 2H); 7.39 (m, 5H); 7.50 (m, 2H); 7.62 (m, 1H); 8.12 (d, 2H).

Preparation No. 34: Preparation of 13-(N-(4-tetrapyranyloxycarbonyl)- β -phenyl isoserinyl)-
30 baccatin III (10GA)

13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A, 10 mg, 0.013 mM) is treated with 4-tetrahydropyranol succinimidyl carbonate (3.3 mg, 0.014 mM), pyridine (5 μ L) and methylene chloride (100 μ L). The mixture is stirred overnight at room temperature. The reaction is diluted with ethyl acetate and washed with 5% aqueous sodium bisulfate and 5%
35 aqueous sodium bicarbonate. The ethyl acetate solution is dried and evaporated, giving 10.3 mg crude product. Purification by column chromatography on silica gel in (40-60) acetone-hexane

yields pure 13-(N-(4-tetrapyranyl-oxycarbonyl)- β -phenyl isoserinyl)-baccatin III (10GA).

TLC: silica gel 60; 40-60 acetone hexane; Rf: 0.17.

^1H NMR (CDCl_3 , TMS) δ 1.15 (s); 1.27 (s); 1.5-1.8 (m); 1.68 (s); 1.84 (s); 1.89 (m); 2.1-2.4 (m); 2.25 (s, 3H); 2.41 (s, 3H); 2.49 (d, 1H); 2.55 (m, 1H); 3.08 (m, 1H); 3.27 (m, 1H); 3.33 (d, 1H); 3.70 (m, 1H); 3.80 (d+m, 2H); 4.16 (d, 1H); 4.29 (d, 1H); 4.42 (m, 1H); 4.66 (m, 2H); 4.94 (d, 1H); 5.33 (m, 1H); 5.57 (m, 1H); 5.65 (d, 1H); 6.28 (s+m, 2H); 7.37 (m, 5H); 7.51 (m, 2H); 7.61 (m, 1H); 8.14 (d, 2H).

Preparation No. 35 Preparation of 13-(N-(tert-butylacetyl)- β -phenyl isoserinyl)-baccatin III (10HA) and 2'-t-butylacetyl-13-(N-(tert-butylacetyl)- β -phenyl isoserinyl)-baccatin III (12CA)

A 51 mg (0.068 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) is stirred under nitrogen at 0°C in 1 mL dry pyridine. A 0.01 mL quantity (9.1 mg, 0.068 mM) of tert-butylacetyl chloride is dissolved in 0.1 mL methylene chloride. This solution is added dropwise to the starting amine. The reaction is allowed to react at 0°C for 3 hours and in the freezer overnight.

The reaction is diluted with ethyl acetate and washed with 1N HCl and 5% sodium bicarbonate. The aqueous layers are backextracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum.

The crude product is chromatographed over 7 g silica gel, eluting with 50-50 and 70-30 EtOAc-hexane. Fractions of 2 mL are collected, analyzing them by TLC. The following fractions are combined and evaporated under vacuum.

Fr. 11-21, impure 2'-t-butylacetyl-13-(N-(tert-butylacetyl)- β -phenyl isoserinyl)-baccatin III (12CA)

Fr. 22-45, 13-(N-(tert-butylacetyl)- β -phenyl isoserinyl)-baccatin III (10HA), white solid.

12CA is still impure and is rechromatographed over 3 g silica gel, eluting with 10-90 acetone-methylene chloride. Fractions of 1 mL are collected, analyzing them by TLC. Fractions 11-28 contained the product and are combined and evaporated under vacuum to give pure 2'-t-butylacetyl-13-(N-(tert-butylacetyl)- β -phenyl isoserinyl)-baccatin III (12CA) as a white solid.

Data for 12CA:

TLC: silica gel 60; 60-40 ethyl acetate - hexane; Rf: 0.70.

Mass Spec (FAB, m/z) ($M+H$) measured at 946.4618; theory for $\text{C}_{52}\text{H}_{68}\text{N}_1\text{O}_{15}$ is 946.4589; 946, 509, 378, 360, 280, 262, 234, 105, 99, 57, 43.

^1H NMR (CDCl_3 , TMS) δ 0.98 (s); 1.28 (s, 3H); 2.23 (s, 3H); 2.42 (s, 3H); 2.53 (m); 3.81 (d, 1H); 4.19 (d, 1H); 4.31 (d, 1H); 4.45 (m, 1H); 4.97 (d, 1H); 5.34 (d, 1H); 5.69 (d, 1H); 5.75 (m, 1H); 6.08 (d, 1H); 6.24 (m, 1H); 6.31 (s, 1H); 7.28-7.45 (m, 5H); 7.51 (t, 2H); 7.61 (t, 1H); 8.11 (d, 2H).

Data for 10HA:

TLC: silica gel 60; 60-40 ethyl acetate - hexane; Rf: 0.27

Mass Spec (FAB, m/z) (M+H) measured at 848.3863; theory for $C_{46}H_{58}N_1O_{14}$ is 848.3857; 848, 830, 788, 770, 569, 551, 509, 280, 262, 234, 182, 136, 115, 105, 99, 57, 43.

1H NMR ($CDCl_3$, TMS) δ 0.97 (s); 1.26 (s, 3H); 2.24 (s, 3H); 2.33 (s, 3H); 2.52 (m, 2H); 3.60 (d, 1H); 3.78 (d, 1H); 4.18 (d, 1H); 4.29 (d, 1H); 4.39 (m, 1H); 4.65 (m, 1H); 4.93 (d, 1H); 5.55 (dd, 1H); 5.67 (d, 1H); 6.19 (t, 1H); 6.28 (s, 1H); 7.39 (m, 5H); 7.50 (t, 2H); 7.62 (t, 1H); 8.10 (d, 2H).

Preparation No. 36: Preparation of 13-(N-(pivaloyl)- β -phenyl isoserinyl)-baccatin III (10IA)

A 44 mg (0.06 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) is stirred at 0°C under nitrogen in 1 mL dry pyridine. To this is added over 5 min a solution of 8 mg (0.06 mM) trimethylacetyl chloride in 0.2 mL methylenechloride. After 30 minutes reaction, TLC shows most of the amine to have reacted.

The reaction is partitioned between 1N HCl-ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate and evaporated under vacuum.

The crude product is chromatographed over 5 g silica gel, eluting with (65-35) EtOAc-hexane. Fractions of 2 mL are collected, analyzing them by TLC. The product is found in fractions 10-38, which upon combining and evaporating under vacuum yields the title compound.

Spectral data indicates the presence of a small amount of pivalic acid. Therefore, the product is dissolved in ethyl acetate, washed with 5% sodium bicarbonate, dried over sodium sulfate and evaporated under vacuum. This yields 10IA, as a white solid.

TLC: silica gel 60; 50-50 EtOAc-hexane; Rf: 0.29.

Mass Spec (FAB, m/z) (M+H) measured at 834.3712; theory for $C_{45}H_{56}N_1O_{14}$ is 834.3700; 834, 816, 774, 569, 551, 509, 387, 327, 266, 248, 220, 190, 105, 57.

1H NMR: ($CDCl_3$, TMS) δ 1.16 (s); 1.23 (s); 2.23 (s, 3H); 2.29 (d, 1H); 2.35 (s, 3H); 2.51 (m, 1H); 3.77 (d, 1H); 4.17 (d, 1H); 4.28 (d, 1H); 4.38 (m, 1H); 4.68 (d, 1H); 4.93 (d, 1H); 5.56 (dd, 1H); 5.66 (d, 1H); 6.17 (m, 1H); 6.28 (s, 1H); 6.54 (d, 1H); 7.35 (m, 5H); 7.49 (m, 2H); 7.60 (m, 1H); 8.10 (d, 2H).

Preparation No. 39 Preparation of 7-Fluoro-13-(N-Cbz- β -phenyl-isoserinyl)-baccatin III (18) from 7-Fluoro-13-(N-Cbz- β -phenyl-isoserinyl)-2'-troc-baccatin III (13BA)

A solution of 7-fluoro-13-(N-Cbz- β -phenyl-isoserinyl)-2'-troc-baccatin III (13BA, Example 3) (0.079 g) in 9:1 methanol/acetic acid (20 mL) and ethyl acetate (8mL) is stirred with activated zinc (0.153 g) at room temperature for two hours. Following workup, the crude product is chromatographed over silica gel using 40% EtOAc-hexane for elution to give 7-fluoro-13-(N-Cbz- β -phenyl-isoserinyl)-baccatin III (18): mass spectrum, 886, 571, 511, 371, 347, 329, 316, 298, 105, 91 m/z .

Preparation No. 40: Preparation of 7-Fluoro-13-(β -phenyl isoserinyl)-baccatin III (19)

A 23.5 mg (0.027 mM) quantity 7-Fluoro-13-(N-Cbz- β -phenyl isoserinyl)-baccatin III (Preparation No. 39, 18,) is dissolved in 3 mL absolute ethanol and the solution treated with 7 mg 10% Pd/C and hydrogenated at atmospheric pressure and room temperature for 4.5 hours.

- 5 The disappearance of starting material is followed by TLC. The reaction is filtered through Celite, washing the Celite with ethyl acetate. The combined filtrate and wash are evaporated under vacuum. The residue is treated twice with ethyl acetate-hexane and evaporated under vacuum. This yields 7-Fluoro-13-(β -phenyl isoserinyl)-baccatin III (19) as a white solid.

TLC: silica gel 60; 50-50 ethyl acetate -hexane; Rf: 0.11.

- 10 ^1H NMR (CDCl_3 , TMS): δ 2.20 (s, 3H); 2.26 (s, 3H); 2.54 (m, 1H); 3.99 (d, 1H); 4.24 (d, 1H); 4.27-4.42 (m, 3H); 4.55 (dd, $J=48$ Hz, $J=5$ Hz, 1H); 4.99 (d, 1H); 5.72 (d, 1H); 6.11 (m, 1H); 6.55 (s, 1H); 7.27 (s, 1H); 7.39 (m, 4H); 7.51 (m, 2H); 7.64 (m, 1H); 8.08 (d, 2H).

Preparation No. 41: Preparation of 7-Fluoro-13-(N-Boc- β -phenyl isoserinyl)-baccatin III (20) and 7-Fluoro-2'-Boc-13-(N-Boc- β -phenyl isoserinyl)-baccatin III (13CA)

- 15 A 0.027 mM quantity 7-Fluoro-13-(β -phenyl isoserinyl)-baccatin III (Preparation No. 40; 19) is dissolved with stirring in 0.2 mL freshly distilled THF at room temperature and under nitrogen. Add 6 mg (0.027 mM) di-tert-butyl dicarbonate and 0.004 mL (0.029 mM) triethylamine. Left to react for 20 hours.

- 20 The reaction is partitioned between ethyl acetate-brine. The layers are separated and the aqueous layer reextracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum.

- The product mixture is chromatographed over 3 g silica gel, eluting with 30-70 ethyl acetate-hexane until the first product comes off and then switching to 50-50 ethyl acetate-hexane. Fractions of 1 mL are collected, analyzing them by TLC. The following fractions are
25 combined and evaporated to leave white solids.

Fr. 16-30, 13CA

Fr. 32-46, 20

Data for 13CA:

TLC: silica gel 60; 50-50 ethyl acetate-hexane; Rf: 0.83

- 30 Mass Spec (FAB, m/z) 952 ($M+H$), 878, 822, 778, 571, 511, 389, 329, 106, 162, 105, 57.

- ^1H NMR (CDCl_3 , TMS): δ 1.17 (s, 3H); 1.24 (s, 3H); 1.25 (s, 9H); 1.90 (s, 9H); 2.08 (s, 3H); 2.22 (s, 3H); 2.0-2.7 (m, 4H); 4.02 (d, 1H); 4.24 (d, 1H); 4.36 (d, 1H); 4.59 (dd, $J=48$ Hz, $J=5$ Hz, 1H); 4.77 (bs, 1H); 5.02 (d, 1H); 5.22 (bs, 1H); 5.68 (m, 1H); 5.77 (d, 1H); 6.27
35 (m, 1H); 6.57 (s, 1H); 7.27-7.70 (m, 9H); 8.09 (d, 2H).

Data for 20:

TLC: silica gel 60; 50-50 ethyl acetate-hexane; Rf: 0.54

Mass Spec (FAB, m/z): (M+H) measured at 852.3638; theory for $C_{45}H_{55}F_1N_1O_{14}$ is 852.3606; 852, 796, 752, 692, 674, 571, 511, 389, 347, 329, 105, 57, 43.

1H NMR ($CDCl_3$, TMS): δ 1.17 (s, 3H); 1.23 (s, 3H); 1.34 (s, 9H); 2.22 (s, 3H); 2.39 (s, 3H); 2.0-2.7 (m, 4H); 3.36 (m, 1H); 4.04 (d, 1H); 4.28 (d, 1H); 4.37 (d, 1H); 4.48-4.68 (m, 2H); 5.01 (d, 1H); 5.30 (m, 1H); 5.45 (m, 1H); 5.76 (d, 1H); 6.21 (m, 1H); 6.56 (s, 1H); 7.30-7.70 (m, 9H); 8.13 (d, 2H).

Preparation No. 42 Preparation of 13-(N-Benzoyloxycarbonyl- β -phenyl-isoserinyl)-7-deoxy-7 β ,8 β -methanobaccatin III (21) from 13-(N-Benzoyloxycarbonyl- β -phenyl-isoserinyl)-2'-trac-7-deoxy-7 β ,8 β -methanobaccatin III (14BA)

A solution of 13-(N-benzoyloxycarbonyl- β -phenyl-isoserinyl)-2'-trac-7-deoxy-7 β ,8 β -methanobaccatin III (14BA, Example 3) (0.040 g) in 9:1 methanol/acetic acid (10 mL) is stirred at room temperature with activated zinc (0.144 g) for 3 hours. Following workup, the crude reaction product is chromatographed over silica gel using 40% EtOAc-hexane for elution to give 13-(N-benzoyloxycarbonyl- β -phenyl-isoserinyl)-7-deoxy-7 β ,8 β -methanobaccatin III (21):

mass spectrum,

found: 866.3423, $C_{48}H_{51}NO_{14}$ + H requires 866.3388, 848, 806, 788, 551, 533, 491, 105, 91 m/z .

Preparation No. 43: Preparation of 13-(β -phenyl isoserinyl)-7-deoxy-7 β ,8 β -methanobaccatin III (22)

A 14 mg (0.016 mM) quantity of 13-(N-benzoyloxycarbonyl- β -phenyl isoserinyl)-7-deoxy-7 β ,8 β -methanobaccatin III (Preparation No. 42, 21) is dissolved in 2 mL absolute ethanol. Add 5 mg 10% Pd/C and hydrogenate at room temperature and atmospheric pressure for 6 hours. The reaction is followed by TLC and upon completion is filtered through Celite, washing with ethyl acetate. The filtrate and wash is combined and evaporated under vacuum. Add ethyl acetate-hexane twice, reevaporating, to give 22 as a white solid. Stored in freezer overnight to be used as is in Preparation No. 44.

TLC: silica gel 60; 50-50 EtOAc-hexane; Rf: streak from origin partly up the plate.

1H NMR ($CDCl_3$, TMS) δ 5.62 (d, 1H); 6.11 (t, 1H); 6.31 (s, 1H); 7.39 (m); 7.53 (m, 2H); 7.66 (m, 1H); 8.08 (d, 2H).

Preparation No. 44: Preparation of 13-(N-Boc- β -phenyl isoserinyl)-7-deoxy-7 β ,8 β -methanobaccatin III (23) and 13-(N-Boc-2'-Boc- β -phenyl isoserinyl)-7-deoxy-7 β ,8 β -methanobaccatin III (14CA)

A 0.016 mM quantity of 22 (Preparation No. 44) is dissolved with stirring under nitrogen in 0.12 mL dry THF. To this is added 3.5 mg (0.016 mM) di-*t*-butyl dicarbonate in 0.05 mL dry THF and 0.0025 mL (0.018 mM) triethyl amine in 0.015 mL dry THF. Left to

react for 27 hours, when TLC shows the reaction to be fairly complete.

The reaction mixture is partitioned between ethyl acetate-brine. The layers are separated and the aqueous layer reextracted with ethyl acetate. The combined organic layers are dried over sodium sulfate and evaporated under vacuum.

- 5 The crude product mixture is chromatographed over 3 g silica gel. Eluted with a gradient of 30-70 to 50-50 EtOAc-hexane. Fractions of 1 mL are collected, analyzing them by TLC. The following fractions are combined and evaporated, giving white solids.

Fr. 16-30, 14CA

Fr. 33-53, 23

- 10 23 is not quite pure and is rechromatographed over 1 g silica gel, eluting with a gradient of 40-60 to 50-50 EtOAc-hexane. Fractions of 0.5 mL were collected and analyzed by TLC. Pure product is found in fractions 11-20, which upon combining and evaporating under vacuum leave the desired product as a white solid 4 mg.

Data for 14CA:

- 15 TLC: silica gel 60; 50-50 EtOAc-hexane; Rf: 0.87

Mass Spec (FAB, m/z) 858, 803, 798, 551, 491, 369, 327, 206, 105, 57.

^1H NMR: (CDCl_3 , TMS) δ 1.25 (s); 2.01 (s, 3H); 2.21 (s, 3H); 2.43 (m); 4.01 (d, 1H); 4.07 (d, 1H); 4.28 (d, 1H); 4.70 (m, 2H); 5.18 (bs, 1H); 5.64 (m, 2H); 6.25 (m, 1H); 6.33 (s, 1H); 7.39 (m, 5H); 7.51 (m, 2H); 7.64 (m, 1H); 8.09 (d, 2H).

- 20 Data for 23 :

TLC: silica gel 60; 50-50 EtOAc-hexane; Rf: 0.77

Mass Spec (FAB, m/z) : (M+H) measured: 832.3588; theory for $\text{C}_{45}\text{H}_{54}\text{N}_1\text{O}_{14}$ is 832.3544; 832, 814, 776, 732, 714, 696, 672, 551, 491, 105, 57.

- ^1H NMR: (CDCl_3 , TMS) δ 1.28 (s); 1.37 (m); 1.68 (m); 1.85 (s); 2.10 (m); 2.21 (s, 25 3H); 2.26 (m); 2.39 (s, 3H); 2.47 (m); 3.30 (m, 1H); 4.06 (m, 2H); 4.31 (d, 1H); 4.63 (m, 1H); 4.74 (d, 1H); 5.30 (m, 1H); 5.36 (d, 1H); 5.66 (d, 1H); 6.28 (m, 1H); 6.33 (s, 1H); 7.37 (m, 5H); 7.51 (m, 2H); 7.61 (m, 1H); 8.15 (d, 2H).

Preparation No. 45: Preparation of 13-(N-phenyl urea- β -phenyl-isoserinyl)-baccatin III; 13-(β -phenyl-isoserinyl)-baccatin III N-phenyl urea (10JA)

- 30 A 48 mg (0.064 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) is dissolved in 700 μL THF and 6.5 μL (0.060 mM) phenyl isocyanate added. TLC shows no amine remained. The solution is diluted with EtOAc and extracted with sat. CuSO_4 . The organic layer is filtered through Na_2SO_4 and concentrated in vacuo and chromatographed over 5gm of silica gel packed in 1:1 EtOAc:Hexane. The column is eluted with 20 mL 1:1
35 EtOAc:Hexane, 20 mL 3:2 EtOAc:Hexane, and 20 mL 2:1 EtOAc:Hexane collecting 3 mL fractions. The desired product is found in fractions 17-31.

-47-

Mass Spec (FAB-High Res.) Theory: 869.3496 Found: 869.3512

¹H NMR (CDCl₃; TMS): δ 1.13 (s,3H); 1.19 (s,3H); 1.81 (s,3H); 2.19 (s,3H); 2.27 (m); 2.37 (s,3H); 2.51 (m,1H); 2.66 (m,1H); 3.76 (d,1H); 4.18 (d,1H); 4.28 (d,1H); 4.37 (m,1H); 4.67 (m,1H); 4.93 (d,1H); 5.49 (dd,1H); 5.67 (d,1H); 6.21 (m,1H); 6.27 (s,1H); 6.93 (m,2H); 7.07 (m,2H); 7.19 (m,3H); 7.26-7.40 (m); 7.48 (m,1H); 7.60 (m,1H); 8.10 (d,2H)

Preparation No. 46: Preparation of N-debenzoyl-N-(*t*-butyl)aminocarbonyl-taxol; 13-β-phenyl-isoserinyl)-baccatin III N-*t*-butyl urea (10KA)

N-debenzoyl-N-(*t*-butyl)aminocarbonyl-taxol (51 mg, 0.07 mM; Preparation No. 24, 11A) is dissolved in 700 μL THF and 7 μL (0.061 mM) *t*-butyl isocyanate is added. TLC shows some amine remaining so another 3 μL is added. This is repeated twice more until TLC shows little amine left (3 μL and 4 μL). The solution is concentrated in vacuo and the residue chromatographed over 5 gm of silica gel packed in 1:1 EtOAc:hexane. The column is eluted with 50 mL 1:1 EtOAc:hexane, 25 mL 3:2 EtOAc:hexane, and 25 mL 2:1 EtOAc:hexane collecting 3 mL fractions. The desired product is found in fractions 21-40.

Mass Spec (FAB-High Res.) Theory: 849.3809 Found: 849.3809

¹H NMR (CDCl₃; TMS): δ 1.14 (s,3H); 1.22 (s); 1.24 (s); 1.83 (s,3H); 2.23 (s,3H); 2.44 (s,3H); 2.50 (m,1H); 3.77 (d,1H); 4.17 (d,1H); 4.29 (d,1H); 4.38 (m,1H); 4.61 (m,1H); 4.94 (d,1H); 5.29 (m,2H); 5.67 (d,1H); 6.18 (m,1H); 6.29 (s,1H); 7.33 (m,5H); 7.49 (m,1H); 7.61 (m,1H); 8.09 (d,2H)

Preparation No. 47: Preparation of 13-(N-1-methyl-1-cyclohexamide-β-phenyl-isoserinyl)-baccatin III; 13-(N-(1-methyl-1-cyclohexanoyl)-β-phenyl-isoserinyl)-baccatin III (10MA)

A 30 mg (0.04 mM) quantity of 13-(β-phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) is dissolved in 400 μL pyridine and cooled to 0°C. Once cooled 20 μL of 300 mg per 1 ml of 1-methyl-1-cyclohexyl carbonyl chloride in CH₂Cl₂ (0.037mM) is added. TLC showed some amine remained so another 10 μL added. TLC shows little amine left. The solution is diluted with EtOAc and extracted with sat. CuSO₄. The organic layer is filtered through Na₂SO₄ and concentrated in vacuo and chromatographed over 3 gm of silica gel packed in 1:1 EtOAc:Hexane. The column is eluted with 50 mL 1:1 EtOAc:Hexane and 20 mL 3:2 EtOAc:Hexane collecting 2 mL fractions. The desired product is found in fractions 11-28.

Mass Spec (FAB-High Res.) Theory: 874.4013 Found: 874.4011

¹H NMR (CDCl₃; TMS): δ 1.12 (s,3H); 1.15 (s,3H); 1.26 (s,3H); 1.81 (s,3H); 1.87 (m,3H); 2.24 (s,3H); 2.36 (s,3H); 2.54 (m,1H); 3.78 (d,1H); 4.18 (d,1H); 4.29 (d,1H); 4.40 (m,1H); 4.70 (d,1H); 4.94 (d,1H); 5.61 (dd,1H); 5.67 (d,1H); 6.19 (m,1H); 6.28 (s,1H); 6.51 (d,1H); 7.38 (m,5H); 7.50 (m,2H); 7.61 (m,1H); 8.11 (d,2H)

Preparation No. 48: Preparation of 13-(N-1-phenyl-1-cyclopentamide- β -phenyl-isoserinyl)-baccatin III; 13-(N-(1-phenyl-1-cyclopentanoyl)- β -phenyl-isoserinyl)-baccatin III (10NA)

A 26 mg (0.035 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) is dissolved in 400 μ L pyridine and cooled to 0°C. Once cooled 20 μ L of 350 mg per 1 mL of 1-phenyl-1-cyclopentyl carbonyl chloride in CH_2Cl_2 (0.033 mM) was added. TLC showed some amine remained so another 20 μ L added. TLC showed no amine. The solution is diluted with EtOAc and extracted with sat. CuSO_4 . The organic layer is filtered through Na_2SO_4 and concentrated in vacuo and chromatographed over 3 gm of silica gel packed in 1:1 EtOAc:Hexane. The column is eluted with 50 mL 1:1 EtOAc:Hexane and 25 mL 3:2 EtOAc:Hexane collecting 2 mL fractions. The desired product is found in fractions 12-29.

Mass Spec (FAB-High Res.) Theory: 922.4013 Found: 922.4022

^1H NMR (CDCl_3 ; TMS): δ 1.16 (s,3H); 1.27 (s,3H); 1.77 (s,3H); 1.60-2.10 (m); 2.25 (s,3H); 2.35 (s,3H); 2.25-2.65 (m); 3.75 (d,1H); 4.19 (d,1H); 4.28 (d,1H); 4.38 (m,1H); 4.59 (d,1H); 4.92 (d,1H); 5.49 (dd,1H); 5.66 (d,1H); 6.10 (m,2H); 6.26 (s,1H); 7.08 (m,2H); 7.29 (m); 7.53 (m,2H); 7.63 (m,1H); 8.12 (d,2H)

Preparation No. 49: Preparation of 13-(N-phthalimide- β -phenyl-isoserinyl)-baccatin III; 13-(β -phenyl-isoserinyl)-baccatin III N-phthalimide (10PA)

A 29 mg (0.04 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) is dissolved in 400 μ L pyridine and 15 mg (0.07mM) carbethoxyphthalimide. The reaction is checked by TLC and after 72 hours no amine is seen. The solution is diluted with EtOAc and extracted with sat. CuSO_4 . The organic layer is filtered through Na_2SO_4 and concentrated in vacuo and chromatographed over 4 gm of silica gel packed in 1:1 EtOAc:Hexane. The column is eluted with 20 mL 1:1 EtOAc:Hexane, 20 mL 3:2 EtOAc:Hexane, 20 mL 2:1 EtOAc:Hexane, and 20 mL 4:1 EtOAc:Hexane collecting 2 mL fractions. The desired product is found in fractions 16-28.

^1H NMR(CDCl_3 ; TMS): δ 1.09 (s,3H); 1.16 (s,3H); 1.81 (s,3H); 2.21 (s,3H); 2.44 (s,3H); 2.52 (m,2H); 3.76 (d,1H); 4.15 (d,1H); 4.28 (d,1H); 4.41 (m,2H); 4.96 (d,1H); 5.31 (m,1H); 5.61 (d,1H); 5.76 (d,1H); 6.08 (m,1H); 6.24 (s,1H); 7.23 (m,1H); 7.36 (m,2H); 7.52 (m,4H); 7.66 (m,1H); 7.80 (m,4H); 8.10 (d,2H)

Preparation No. 50: Preparation of N-debenzoyl-N-(*t*-butyl)aminothiocarbonyl-taxol (10LA)

A 24 mg (0.032 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) is stirred at room temperature under nitrogen in 0.2 mL dry THF. A 4 μ L quantity (0.032 mM) *t*-butyl-isothiocyanate is added. TLC after 5 hours shows the reaction to be incomplete. An additional 4 μ L *t*-butyl-isothiocyanate is added and the reaction allowed to proceed overnight. The crude product is coated on 0.5 g silica gel and chromatographed over 3

g silica gel, eluting with 60-40 ethyl acetate-hexane. Fractions of 1 mL are collected, analyzing them by TLC. Fractions 7-20 contain the product and are combined and evaporated under vacuum to yield the desired product.

TLC: silica gel 60; 60-40 EtOAc-hexane; Rf: 0.40.

5 ^1H NMR (CDCl_3 , TMS) δ 1.14 (s, 3H); 1.40 (s, 9H); 1.80 (s, 3H); 2.25 (s, 3H); 2.40 (s, 3H); 3.50 (s, 1H); 3.80 (d, 1H); 4.23 (m, 2H); 4.40 (bs, 1H); 4.86 (s, 1H); 4.93 (d, 1H); 5.66 (d, 1H); 6.18 (s, 1H); 6.27 (s, 1H); 6.28-6.40 (m, 2H); 6.59 (d, 1H); 7.30-7.54 (m, 7H); 7.58 (t, 1H); 8.09 (d, 2H).

Mass Spec (FAB, m/z) ($\text{M}+\text{H}$) measured at 865.3577; theory for $\text{C}_{45}\text{H}_{57}\text{N}_2\text{O}_{13}\text{S}$ is
10 865.3581; 865, 569, 509, 297, 279, 251, 133, 105, 77, 57.

Preparation No. 51: Preparation of Taxotere (10BF) from 10-Acetyl Taxotere (10BA)

A 25 mg (0.029 mM) quantity of 10-acetyl Taxotere (Preparation No. 1, 10BA) is stirred at room temperature under nitrogen in 1.0 mL 95% ethanol. Add 2 drops anhydrous hydrazine and leave to react for 1.5 hours, when TLC showed the reaction to be mostly
15 complete. The reaction is partitioned between water-methylene chloride. The aqueous layer is backextracted with methylene chloride. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum.

The crude product is chromatographed over 3 g silica gel, eluting with 70-30 ethyl acetate-hexane. Fractions of 1 mL are collected, analyzing them by TLC. Fractions 14-28
20 contain the product and are combined and evaporated under vacuum.

TLC: silica gel 60; 70-30 EtOAc-hexane; Rf: 0.33.

^1H NMR (CDCl_3 , TMS) δ 1.12 (s, 3H); 1.23 (s, 3H); 1.34 (s, 9H); 1.74 (s, 3H); 1.85 (s, 3H); 2.37 (s, 3H); 2.56 (m, 1H); 3.53 (bs, 1H); 3.90 (d, 1H); 4.18 (d, 1H); 4.21 (m, 1H); 4.30 (d, 1H); 4.32 (s, 1H); 4.62 (bs, 1H); 4.94 (d, 1H); 5.23 (s, 1H); 5.28 (bs, 1H); 5.52 (d, 1H); 5.66 (d, 1H); 6.20 (t, 1H); 7.25-7.45 (m, 6H); 7.50 (t, 2H); 7.61 (t, 1H); 8.11 (d, 2H).
25

Preparation No. 52: Preparation of 13-(β -phenyl-isoserinyl)-baccatin III N-t-amylurethane (10RA)

Part A: Preparation of t-amyl 4-nitrophenyl carbonate

A solution of t-amyl alcohol (0.54 mL, 5.0 mM) in pyridine (1 mL) was treated at 0°C
30 with 4-nitrophenyl chloroformate (1.00 g, 4.97 mM). After adding 1.5 mL of methylene chloride, the reaction was stirred at room temperature overnight. The reaction was diluted with toluene and filtered. Impurities crystallized out from methylene chloride-hexane.

NMR δ 0.981 (t, 3H); 1.54 (s, 6H); 1.88 (q, 2H); 7.36 (d, 2H); 8.28 (d, 2H).

Part B:

35 A 29 mg (0.039 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No.

24; 11A) and t-amyl 4-nitrophenyl carbonate (13 mg, 0.051 mM) in pyridine (0.10 mL) are stirred at room temperature 3 days. The reaction is diluted with ethyl acetate and washed with 5% aqueous sodium bisulfate. The ethyl acetate solution is dried over anhydrous sodium sulfate, evaporated, and chromatographed on a column of silica gel (3 g, 230-400 mesh). The column is eluted with ethyl acetate-hexane mixtures. The desired product is not completely pure, and is therefore rechromatographed in an acetone-hexane system.

NMR (CDCl₃, TMS): δ 0.86 (t, 3H); 1.15 (s, 3H); 1.27 (s, 3H); 1.29 (s, 3H); 1.30 (s, 3H); 1.68 (s, 3H); 1.85 (s+m, 4H); 2.25 (s+m, 4H); 2.38 (s, 3H); 2.53 (m, 2H); 3.37 (d, 1H); 3.80 (d, 1H); 4.17 (d, 1H); 4.30 (d, 1H); 4.41 (m, 1H); 4.63 (m, 1H); 4.95 (d, 1H); 5.30 (m, 1H); 5.40 (m, 1H); 5.67 (d, 1H); 6.24 (m, 1H); 6.29 (s, 1H); 7.31-7.68 (m, 8H); 8.11 (d, 2H).

¹³C-NMR (CDCl₃, TMS): 8.16, 9.53, 14.85, 20.85, 21.86, 22.61, 25.25, 25.71, 25.91, 26.73, 33.22, 35.42, 35.56, 43.18, 45.59, 56.05, 58.53, 72.14, 72.36, 73.57, 74.94, 75.55, 76.44, 79.03, 79.28, 81.05, 82.68, 84.37, 126.67, 128.05, 128.68, 128.84, 128.91, 130.16, 132.95, 133.69, 138.28, 142.28, 155.25, 167.03, 170.16, 171.27, 172.92, 203.66.

MS (FAB): (m+H)⁺ = 864. Major ions m/z 794, 569, 527, 509, 345, 327.

Preparation No. 53: Preparation of 13-(β -phenyl-isoserinyl)-baccatin III N-neopentylurethane (10UA)

Part A: Preparation of Neopentyl 4-Nitrophenyl Carbonate

A solution of neopentyl alcohol (0.54 ml, 5.01 mM), pyridine (1 mL), 4-nitrophenyl chloroformate (1.00 g, 5.0 mM), and distilled THF (2 mL) in a flame-dried flask is stirred at room temperature 40 h. The reaction is diluted with hexane, filtered and evaporated. The product is chromatographed on silica gel in ethyl acetate-hexane mixtures. The product which elutes from the column is further purified by recrystallization from methylene chloride-hexane.

NMR (CDCl₃, TMS): δ 1.02 (s, 9H); 3.99 (s, 2H); 7.39 (d, 2H); 8.29 (d, 2H).

Part B:

A 20 mg (0.027 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) and neopentyl 4-nitrophenyl carbonate (7.4 mg, 0.031 mM) in pyridine (80 μ l) is stirred at room temperature overnight. The reaction is diluted with ethyl acetate and washed 5% aqueous sodium bisulfate. The organic solution is dried over anhydrous sodium sulfate and concentrated. The crude product is chromatographed twice on silica gel, first in acetone-hexane, then in ethyl acetate-hexane mixtures to yield the desired product.

NMR (CDCl₃, TMS): δ 0.82 (s, 9H); 1.15 (s, 3H); 1.26 (s, 3H); 1.68 (s, 3H); 1.84 (s+m, 4H); 2.25 (s+m, 4H); 2.38 (s, 3H); 2.52 (m, 2H); 3.40 (d, 1H); 3.61 (d, 1H); 3.72 (m, 1H); 3.79 (d, 1H); 4.18 (d, 1H); 4.29 (d, 1H); 4.41 (m, 1H); 4.66 (m, 1H); 4.94 (d, 1H); 5.33 (m, 1H); 5.59 (m, 1H); 5.66 (d, 1H); 6.28 (s+m, 2H); 7.30-7.70 (m, 8H); 8.12 (d, 2H).

¹³C-NMR (CDCl₃, TMS): 9.45, 14.74, 20.73, 21.79, 22.47, 26.09, 26.72, 31.32, 35.46.

-51-

43.05, 45.50, 56.38, 58.45, 72.03, 73.47, 74.57, 75.42, 76.36, 79.02, 81.00, 84.28, 126.61, 128.09, 128.58, 128.79, 128.96, 130.11, 132.97, 133.61, 138.10, 141.97, 156.30, 166.91, 170.23, 171.14, 172.47, 203.50.

MS (FAB): $(m+H)^+ = 864$. Major ions m/z 569, 551, 509, 327, 296, 250.

- 5 Preparation No. 54: Preparation of 13-(β -phenyl-isoserinyl)-baccatin III N-(2-chloro-1,1-dimethylethyl)urethane (10SA)

Part A:

- 10 A solution of 1-chloro-2-methyl-2-propanol (0.51 mL, 5.0 mM), 4-nitrophenyl chloroformate (0.999 g, 5.00 mM), pyridine (400 μ L, 5.0 mM), and THF (2 mL) in a dry flask is stirred at room temperature 40 h. The reaction is diluted with hexane and filtered. The filtrate is evaporated and recrystallized from methylene chloride-hexane to yield the desired product.

NMR ($CDCl_3$, TMS): δ 1.64 (s, 6H); 3.87 (s, 2H); 7.38 (d, 2H); 8.28 (d, 2H).

Part B:

- 15 A 28 mg (0.037 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) and chloro-*t*-butyl 4-nitrophenyl carbonate (12.0 mg, 0.044 mM) in pyridine (0.10 ml) is stirred at room temperature overnight. The reaction is diluted with ethyl acetate and washed with 5% aqueous sodium bisulfate. The organic layer is dried over anhydrous sodium sulfate and evaporated. The crude product is purified by column chromatography on silica gel in
20 acetone-hexane mixtures.

NMR ($CDCl_3$, TMS): δ 0.82 (s, 9H); 1.15 (s, 3H); 1.26 (s, 3H); 1.68 (s, 3H); 1.84 (s+m, 4H); 2.25 (s+m, 4H); 2.38 (s, 3H); 2.52 (m, 2H); 3.40 (d, 1H); 3.61 (d, 1H); 3.72 (m, 1H); 3.79 (d, 1H); 4.18 (d, 1H); 4.29 (d, 1H); 4.41 (m, 1H); 4.66 (m, 1H); 4.94 (d, 1H); 5.33 (m, 1H); 5.59 (m, 1H); 5.66 (d, 1H); 6.28 (s+m, 2H); 7.30-7.70 (m, 8H); 8.12 (d, 2H).

- 25 ^{13}C -NMR ($CDCl_3$, TMS): 9.45, 14.74, 20.73, 21.79, 22.47, 26.09, 26.72, 31.32, 35.46, 43.05, 45.50, 56.38, 58.45, 72.03, 73.47, 74.57, 75.42, 76.36, 79.02, 81.00, 84.28, 126.61, 128.09, 128.58, 128.79, 128.96, 130.11, 132.97, 133.61, 138.10, 141.97, 156.30, 166.91, 170.23, 171.14, 172.47, 203.50. MS (FAB): $(m+H)^+ = 864$. Major ions m/z 569, 551, 509, 327, 296, 250.

- 30 Preparation No. 55: Preparation of 13-(β -phenyl-isoserinyl)-baccatin III N-(3-Methyl-3-pentyl)urethane (10TA)

Part A: Preparation of 3-Methyl-3-pentyl 4-Nitrophenyl Carbonate

- 35 A mixture of 3-methyl-3-pentanol (0.62 mL, 5.0mM), 4-nitrophenyl chloroformate (1.01 g, 5.0 mM), THF (2 mL), and pyridine (1 mL) is stirred at room temperature 40 h. Acetonitrile (2 mL) is added and stirring continued overnight. The reaction is diluted with methylene chloride and hexane, filtered and evaporated. The product is chromatographed on silica gel in

ethyl acetate-hexane mixtures.

NMR (CDCl₃, TMS): δ 0.95(t, 6H); 1.50 (s, 3H); 1.90 (m, 4H); 7.35(d, 2H); 8.27 (d, 2H).

Part B:

5 A 32 mg (0.043 mM) quantity of 13-(β -phenyl-isoserinyl)-baccatin III (Preparation No. 24; 11A) and 3-methyl-3-pentyl 4-nitrophenyl carbonate (12.5 mg, 0.047 mM) in pyridine (0.15 mL) is stirred at room temperature 60 h. The reaction is diluted with ethyl acetate and washed with 5% aqueous sodium bisulfate, dried over anhydrous sodium sulfate and evaporated. The product is purified by column chromatography on silica gel in acetone-hexane mixtures.

10 NMR (CDCl₃, TMS): δ 0.76 (t, 6H); 1.15 (s, 3H); 1.24 (s, 3H); 1.27 (s, 3H); 1.50-1.98 (3 s + m, 12H); 2.25 (s + m, 5H); 2.38 (s, 3H); 2.53 (m, 2H); 3.37 (bs, 1H); 3.80 (d, 1H); 4.17 (d, 1H); 4.30 (d, 1H); 4.41 (m, 1H); 4.64 (m, 1H); 4.95 (d, 1H); 5.29 (m, 1H); 5.42 (m, 1H); 5.66 (d, 1H); 6.24 (m, 1H); 6.29 (s, 1H); 7.30-7.70 (m, 8H); 8.11 (d, 2H).

¹³C-NMR (CDCl₃, TMS): 7.61, 9.27, 14.58, 20.58, 21.63, 22.35, 22.58, 26.46, 30.18, 30.26, 35.15, 35.29, 42.91, 45.31, 55.68, 58.26, 71.88, 72.13, 73.27, 74.71, 75.29, 76.31, 78.78, 80.79, 84.10, 84.95, 126.38, 127.77, 128.41, 128.58, 128.81, 129.90, 132.71, 133.41, 138.06, 142.03, 154.86, 166.70, 169.88, 171.00, 172.68, 203.40. MS (FAB): (m+H)⁺ = 878. Major ions m/z 794, 569, 527, 509, 345, 327.

Preparation No. 56 Preparation of N-(t-butylaminocarbonyl)- β -phenyl isoserine methyl ester

20 (3K)

(2R,3S)- β -phenyl-isoserine methyl ester (4.35g, 22 mM) is dissolved in 100mL dry THF and the flask cooled to 0 °C. To the solution is added t-butyl isocyanate (2.8 mL, 25mM). TLC after 15 minutes shows some starting material left so another 0.5 mL of the isocyanate is added. TLC after 1 hour shows no starting material so the solvent is concentrated in vacuo leaving N-(t-butylaminocarbonyl)- β -phenyl isoserine methyl ester (3K).

Proton NMR (CDCl₃, TMS): δ 1.27 (s, 9H); 3.43 (d, 1H); 3.81 (s, 3H); 4.34 (br s, 1H); 4.48 (m, 1H); 5.27 (m, 1H); 5.32 (m, 1H); 7.29 (m, 2H); 7.34 (m, 3H)

Mass spec (FAB-High Res.) Theory for C₁₅H₂₂N₂O₄+H: 295.1658 Found: 295.1663

Preparation No. 57 Preparation of (4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-

30 4-phenyl-5-oxazolidinecarboxylic acid methyl ester (5Ka & 5Kb)

N-(t-butylaminocarbonyl)- β -phenyl-isoserine methyl ester (68 mg, 0.23 mM; 3K, Preparation No. 56) is dissolved in 5 mL dry THF and the solution treated with 2,4-dimethoxy benzaldehyde dimethyl acetal (70 mg, 0.33 mM) and pyridinium p-toluenesulfonate (6 mg, 0.02 mM) and the solution warmed to reflux. Approximately 2 mL solvent is boiled away 3 times in a 45 minute period replenishing with 2 mL of fresh THF at which time TLC shows no starting material. The solvent is concentrated in vacuo and chromatographed over 7 gm of silica

gel packed in 1:3 EtOAc:Hexane. The column is eluted with 80 mL 1:3 EtOAc:Hexane, 45 mL 1:2 EtOAc:Hexane, 30 mL 2:3 EtOAc:Hexane, and 30 mL 1:1 EtOAc:Hexane collecting 3 mL fractions.

- A less polar isomer, (4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (5Ka) is found in fractions 21-31.

Proton NMR (CDCl₃, TMS): δ 1.19 (s,9H); 3.82 (s,3H); 3.85 (s,3H); 3.89 (s,3H); 4.68 (br s,1H); 4.88 (d,1H); 5.52 (d,1H); 6.46 (m); 6.70 (s,1H); 7.25-7.50 (m)

Mass spec (FAB-High Res.): Theory for C₂₄H₃₁N₂O₆+H: 443.2182 Found: 443.2172

- A more polar isomer, (4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (5Kb) is found in fractions 33-42.

Proton NMR (CDCl₃, TMS): δ 0.99 (m,9H); 3.53 (m,3H); 3.81 (m,3H); 3.88 (m,3H); 4.05 (m,1H); 4.55 (m,1H); 5.45 (m,1H); 6.48 (m,2H); 6.79 (m,1H); 7.25-7.50 (m)

Mass spec(FAB-High Res.): Theory for C₂₄H₃₁N₂O₆+H: 443.2182 Found: 443.2180

- Preparation No. 58 Preparation of (4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (6Ka) and its free acid (7Ka)

- A 100 mg (0.23 mM) quantity the less polar isomer of (4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid methyl ester (Preparation 57, 5Ka) is stirred at room temperature under nitrogen in 3 mL MeOH. To this is added 0.1 mL water and 43 mg (0.31 mM) potassium carbonate. After 1 hour, TLC shows no starting material left. Store in freezer overnight. The next morning the solvent is evaporated to give (4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (6Ka).

- Proton NMR (d₆-DMSO): δ 1.20 (s, 9H); 3.51 (s, 1H); 3.76 (s, 3H); 3.96 (s, 3H); 4.32 (d, 2H); 4.80 (s, 1H); 5.29 (d, 1H); 6.60-6.68 (m, 2H); 6.71 (d, 1H); 7.26 (d, 1H); 7.35 (s, 1H); 7.45 (t, 2H); 7.53 (d, 2H).

Preparation No. 59 Preparation of (4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid (7Ka)

- (4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid potassium salt (6Ka, Preparation 58) is partitioned between methylene chloride and water containing 0.9 mL 1N HCl. The layers are separated and the aqueous layer reextracted with methylene chloride. The organic layers are combined, dried over sodium sulfate and evaporated. This leaves (4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid (7Ka) as a white solid.

- Preparation No. 60: Preparation of 7-TES-baccatin III-13-(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9KaA)

(4S,5R)-N-(t-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-

oxazolidinecarboxylic acid (1.07 mM, Preparation 59, 7Ka) is dissolved in 1.5 mL methylene chloride-3 mL toluene. To this is added 7-TES-baccatin III (500 mg, 0.71 mM, 8A), DMAP (45 mg, 0.36 mM) and DCC (240 mg, 1.15 mM). The reaction is stirred under nitrogen for one hour at RT. The resultant urea side product is removed by filtration and the filtrate is evaporated under vacuum. The residue is chromatographed over silica gel (80 g), eluting with 25-75 EtOAc-hexane (200 mL) and 33-67 EtOAc-hexane (1 L). Fractions of 20 mL are collected, analyzing them by TLC. Fractions 28-47 contain the desired product and are combined and evaporated. 7-TES -baccatin III-13-(4S,5R)-N-(*t*-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (9KaA) is obtained as a white solid.

10 Mass Spec (FAB, *M*+*H*): Calc'd for $C_{60}H_{79}N_2O_{16}Si$ 1111.5198: Found 1111.5189.
Preparation No. 61: Preparation of 13-(N-(*t*-butylaminocarbonyl)- β -phenyl isoserinyl)-baccatin III; N-debenzoyl-N-(*t*-butyl)aminocarbonyl-taxol; 13- β -phenyl-isoserinyl)-baccatin III N-*t*-butyl urea (10KA)

15 A 0.1 M HCl solution is prepared from 0.071 mL acetyl chloride and 9.929 mL of MeOH, leaving it sit for 30 minutes before using.

7-TES -baccatin III-13-(4S,5R)-N-(*t*-butylaminocarbonyl)-2-(2,4-dimethoxyphenyl)-4-phenyl-5-oxazolidinecarboxylic acid ester (100 mg, Preparation 60, 9KaA) is treated with the above methanolic HCl solution (0.5 mL) with stirring under nitrogen. The reaction is complete after 45 minutes as shown by TLC. The reaction mixture is partitioned between ethyl acetate-20 5% sodium bicarbonate. The layers are separated and the aqueous layer reextracted with ethyl acetate. The organic layers are combined, dried over sodium sulfate and evaporated under vacuum.

The crude product is chromatographed over silica gel (8 g), eluting with 33-67 acetone-hexane (70 mL) and 40-60 acetone-hexane (35 mL). Fractions of 2 mL are collected, analyzing 25 them by TLC. Pure product is found in fractions 18-29, which which are combined and evaporated. 13-(N-(*t*-butylaminocarbonyl)- β -phenyl isoserinyl)-baccatin III (10KA) is obtained as a white solid. The physical data correspond to those obtained previously in Preparation No. 46.

30 PREPARATION 1A 2'-[(2,2,2-Trichloroethyl)oxy]carbonyl]-taxol, 7-Methylxanthate

Methyl iodide (1.3 equivalents) is added to a stirred solution of 2'-[(2,2,2-trichloroethyl)oxy]carbonyl]taxol (1 equivalent) in carbon disulfide. Sodium hydride (2.1 equivalents) is added and the resulting mixture is stirred and checked by tlc for formation of the methyl xanthate. When reaction is complete, the excess carbon disulfide and methyl iodide are 35 removed by evaporation. The residue is partitioned between water and ether, the layers are separated, the organic layer is dried, filtered, and concentrated to give the title compound.

PREPARATION 2A 2'-[[(2,2,2-Trichloroethyl)oxy]carbonyl]taxol, 7-Methanesulfonate

Methanesulfonyl chloride (1.2 equivalents) is added dropwise to a solution of 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]taxol (1 equivalent) and pyridine (5 equivalents) in CH₂Cl₂ which is stirred at ice-bath temperature. The reaction mixture is allowed to warm and stirring is continued until tlc evidence indicates that reaction is complete. The reaction mixture is quenched with ice water and is extracted with CH₂Cl₂ and these extracts are washed successively with dilute aqueous acid, dilute aqueous NaHCO₃, and water and then are dried, filtered, and concentrated to give the crude reaction product. Chromatography of the crude product over silica gel gives pure title compound.

10

PREPARATION 3A 2'-[[(2,2,2-Trichloroethyl)oxy]carbonyl]taxol, 7-Trifluoromethylsulfonate

Trifluoromethanesulfonic anhydride (1.3 equivalents) is added dropwise to a solution of 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]taxol (1 equivalent) in pyridine which is stirred and cooled to -30°C. The reaction mixture is allowed to warm and stirring is continued until tlc evidence indicates the reaction is complete. The reaction solution is quenched with ice water and is extracted with CH₂Cl₂. The CH₂Cl₂ extracts are washed successively with cold, dilute aqueous acid, dilute aqueous NaHCO₃, and water and then are dried, filtered, and concentrated to give the crude reaction product. Chromatography of the crude product over silica gel gives pure title compound.

20

PREPARATION 4A 2'-[[(2,2,2-Trichloroethyl)oxy]carbonyl]-7-deoxy-7-azidotaxol

A solution of 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-taxol, 7-trifluoromethylsulfonate (1 equivalent) and 18-crown-6 (1 equivalent) N,N-dimethylpropylene urea is stirred with potassium azide (10 equivalents). The mixture is stirred and warmed until tlc evidence indicates the reaction is complete. The reaction mixture is quenched with cold water and the resulting solution is extracted with ether. The ether extract is washed thoroughly with water, dried, filtered, and concentrated to give the crude reaction product. Chromatography of the crude product over silica gel gives pure title compound.

PREPARATION 5A 2'-[[(2,2,2-Trichloroethyl)oxy]carbonyl]-7-deoxy-7-aminotaxol

A solution of 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7-azidotaxol in ethanol is stirred with 10% palladium-on-carbon catalyst in a hydrogen atmosphere. Following reaction, the catalyst is removed by filtration and the filtrate is concentrated to give the crude reaction product. Chromatography of the crude product over silica gel gives pure title compound.

35

PREPARATION 6A Preparation of N-Desbenzoyl-N-benzyloxycarbonyl-2'-[[[(2,2,2-trichloroethyl)oxy]carbonyl]-taxol, (({2aR-[2a α ,4 β ,4a β ,6 β ,9 α ,(α R*, β S*)

11 α ,12 α ,12a,12b α]}- β -(Benzyloxycarbonylamino)- α -[[[(2,2,2-trichloroethoxy)-carbonyl]oxy]benzenepropionic Acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-

- 5 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester)) (12BA); and

N-Desbenzoyl-N-benzyloxycarbonyl-2',7-bis[[[(2,2,2-trichloroethyl)oxy]carbonyl]-taxol,

(({2aR-[2a α ,4 β ,4a β ,6 β ,9 α ,(α R*, β S*),11 α ,12 α ,12a,12b α]}- β -(Benzyloxycarbonylamino)- α -[[[(2,2,2-trichloroethoxy)-carbonyl]oxy]benzenepropanoic acid, 6,12b-Bis(acetyloxy)-12-

- 10 (benzoyloxy)-4-[[[(trichloroethoxy)carbonyl]oxy]-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester)).

The procedure described for the preparation of 2'-troc-taxol [Magri et al., J. Org. Chem., 1986, 51, 797] is followed, using N-desbenzoyl-N-benzyloxycarbonyltaxol (0.290 g, 0.328

- 15 mmol) and 2,2,2-trichloroethyl chloroformate (59 μ L, 0.091 g, 0.43 mmol) in CH₂Cl₂ (11 mL) containing pyridine (1.6 mL). Following workup, the crude product (0.340 g) is chromatographed over silica gel (40-63 μ m, Merck size B column) using a CH₂Cl₂ solution for application of the material to the column and 40% EtOAc-hexane (90 fractions), 60% EtOAc-hexane (30 fractions), and EtOAc to elute the column (8 mL fractions are collected).
- 20 N-Desbenzoyl-N-benzyloxycarbonyl-2',7-bistroc-taxol (0.053 g, 13%) is eluted in fractions 14-23. Starting material (0.014 g, 5%) is recovered in fractions 139-143. The desired N-desbenzoyl-N-benzyloxycarbonyl-2'-troc-taxol 12BA (0.248 g, 0.234 mmol, 71%) is eluted in fractions 49-80 and is characterized by the following spectral data:

- ¹H NMR (CDCl₃, TMS) δ 8.15 (d, 2H, aromatic), 7.62 (t, 1H, aromatic), 7.52 (t, 2H, aromatic), 7.30-7.50 (m, 5H, aromatic), 7.17 (m, 2H, aromatic), 6.26 (m, 1H, H₁₃), 6.25 (s, 1H, H₁₀), 5.71 (m, 1H, -NH-), 5.67 (d, 1H, H₂), 5.58 (m, 1H, H₃), 5.41 (d, 1H, H₂), 5.08 (d, 1H, PhCH₂HO-), 4.96 (d, 1H, PhCHH₂O-), 4.94 (m, 1H, H₅), 4.79 (d, 1H, -OCH₂HCCl₃), 4.68 (d, 1H, J = 11.8 Hz, -OCHH₂CCl₃), 4.42 (m, 1H, H₇), 4.31 (d, 1H, H_{20a}), 4.18 (d, 1H, H_{20b}), 3.78 (d, 1H, H₃), 2.55 (m, 1H, H_{6a}), 2.47 (m, 1H, H_{14a}), 2.45 (s, 3H, -CH₃), 2.31 (m, 1H, H_{14b}),
- 30 2.24 (s, 3H, -CH₃), 1.92 (m, 1H, H_{6b}), 1.86 (s, 3H, -CH₃), 1.68 (s, 3H, -CH₃), 1.23 (s, 3H, -CH₃), 1.14 (s, 3H, -CH₃);

mass spectrum 1058, 569, 551, 509, 105, 91 m/z.

PREPARATION 7A 10-Deacetyltaxol

- 35 A solution of taxol (0.026 g, 0.030 mmol) and 98% hydrazine (0.035 g, 1.1 mmol) in 95% ethanol (1.0 mL) is stirred at room temperature for 2 hr. The solution is poured into water and

ether, the mixture is shaken well, and the layers separated. The aqueous layer is extracted with additional ether. The combined ether extracts are dried over Na_2SO_4 , filtered and concentrated, giving 0.021 g of the title compound: ^1H NMR spectrum in CDCl_3 is identical to the spectrum reported for 10-deacetyltaxol (Ringel, I.; Horwitz, S. B. *J. Pharmacol. Exp. Ther.*, **1987**, 242, 692) and is identical to the spectrum of an authentic sample.

PREPARATION 8A 10-Deacetylbaccatin III

A solution of baccatin III (0.024 g, 0.041 mmol) in 95% ethanol (1.0 mL) is prepared by warming the mixture. The solution is cooled to room temperature, 98% hydrazine (0.035 g, 1.1 mmol) is added and the solution is stirred at room temperature for 24 hr. The solution is poured into water/ether, shaken well, and the layers are separated. The ether layer is washed with water, dried (Na_2SO_4), filtered, and concentrated, giving 0.010 g of the title compound: ^1H NMR spectrum in CDCl_3 (sparingly soluble) is identical to that of an authentic sample of 10-deacetylbaccatin III.

PREPARATION 10A N-Debenzoyl-N-[(2,2,2-trichloroethyl)oxy]-carbonyl-2'-triethylsilyltaxol

N-Debenzoyl-N-[(2,2,2-trichloroethyl)oxy]carbonyl]taxol ((13-[N-(2,2,2-trichloroethoxycarbonyl)- β -phenyl-isoserinyl]-baccatin III; **10DA**, Preparation 28)) is selectively silylated by reaction with triethylsilyl chloride in pyridine containing a catalytic amount of 4-dimethylaminopyridine. The reaction is quenched by pouring into ice water and extracting with CH_2Cl_2 . The extract is dried, filtered, concentrated and the crude product is purified by silica gel chromatography, giving the pure title compound.

PREPARATION 13A N-Debenzoyl-N-(*t*-butyl)oxycarbonyl-2'-[(2,2,2-trichloroethyl)oxy]carbonyl]-taxol A (Compound **12DA**); (({2aR-[2a α ,4 β ,4a β ,6 β ,9 α ,(α R*, β S*)-,11 α ,12 α ,12a α ,12b α]}- β -[(*t*-Butyl)oxycarbonylamino]- α -[(2,2,2-trichloroethoxy)carbonyl]oxy} benzenepropionic Acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,-10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz [1,2-b]-oxet-9-yl Ester)); and

N-Debenzoyl-N-(*t*-butyl)oxycarbonyl-2',7-bis{[(2,2,2-trichloro-ethyl)oxy]carbonyl]-taxol (({2aR-[2a α ,4 β ,4a β ,6 β ,9 α ,(α R*, β S*)-,11 α ,12 α ,12a α ,12b α]}- β -[(*t*-Butyl)oxycarbonylamino]- α -[(2,2,2-trichloroethoxy)carbonyl]oxy} benzenepropanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-4-[(trichloroethoxy)carbonyl]oxy)-2a,3,4,4a,5,6,9,10, 11,12,12a,12b-dodecahydro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester)).

Following the procedure for the preparation of 2'-troc-taxol (Magri et al., J. Org. Chem. 1986, 51, 797), but starting with N-debenzoyl-N-(*t*-butyl)oxycarbonyltaxol (Compound 10BA; 1.98 g, 2.33 mmol) and 2,2,2-trichloroethyl chloroformate (405 μ L, 0.622 g, 2.94 mmol) in CH_2Cl_2 (80 mL) the product 12DA is prepared. Following workup, the crude product is

5 chromatographed over silica gel (40-63 μ m, 37 x 350 mm, 190 g) using a CH_2Cl_2 solution for application of the material to the column and 40% EtOAc-hexane (63 fractions) followed by 75% EtOAc-hexane to elute the column (45 mL fractions are collected). N-Debenzoyl-N-(*t*-butyl)oxycarbonyl-2',7-bistroc-taxol (0.140 g) is eluted in fraction 6. Starting material (0.192 g) is recovered in fractions 70-78. The desired N-debenzoyl-N-(*t*-butyl)oxycarbonyl-2'-troc-taxol

10 (Compound 12DA) is eluted in fractions 18-38 and characterized by the following spectral data:

^1H NMR (CDCl_3 , TMS) δ 8.12 (d, 2H, $J = 8.1$ Hz), 7.62 (t, 1H, $J = 7.2$ Hz), 7.51 (t, 2H, $J = 7.7$ Hz), 7.30-7.44 (m, 5H), 6.30 (s, 1H, H_{10}), 6.30 (t, 1H, H_{13}), 5.68 (d, 1H, $J = 7.1$ Hz, H_2), 5.48 (d, 1H, -NH- or H_3), 5.44 (d, 1H, H_3 or -NH-), 5.36 (d, 1H, $J = 2.2$ Hz, H_2), 4.98 (d, 1H, $J = 9.3$ Hz, H_5), 4.79 (d, 2H, $J = 11.9$ Hz, 2'-troc- H_a), 4.70 (d, 2H, $J = 11.8$ Hz, 2'-troc- H_b), 4.44 (m, 1H, H_7), 4.32 (d, 1H, $J = 8.4$ Hz, H_{20a}), 4.18 (d, 1H, $J = 8.4$ Hz, H_{20b}), 3.82 (d, 1H, $J = 6.8$ Hz, H_3)

15

PREPARATION 14A 2'-Triethylsilyl-taxol, 7-methylxanthate

A 500 mg (0.52 mM) quantity of 2'-Triethylsilyl-taxol is dissolved in 5 mL of distilled

20 THF. To the solution is added 50 μ L (0.80 mM) methyl iodide and 155 μ L (2.58 mM) carbon disulfide. A slurry of 40mg (60% sodium hydride in oil) in distilled THF is made and approximately half added and the resulting mixture stirred and checked by tlc for formation of the methyl xanthate. After 0.5 hours the residue is partitioned between saturated NH_4Cl solution and EtOAc, the layers are separated, the organic layer is filtered through Na_2SO_4 , and

25 concentrated to give the title compound. The product is purified by column chromatography using 60 gm of silica gel in 1:4 EtOAc:hexane. The product is added using methylene chloride and the column eluted with 400 mL 1:4 400 mL 1:3 EtOAc:hexane, and 300 mL 1:2 EtOAc:hexane. The fractions containing product are found by TLC and are combined and evaporated giving the 2'-triethylsilyl-taxol, 7-methylxanthate as a white solid.

30 TLC: silica gel 60 ; 33% EtOAc-67% hexane; R_f : 0.40.

NMR (CDCl_3 , TMS): δ 0.44 (m, 6H); 0.81 (m); 1.19 (s, 3H); 1.22 (s, 3H); 2.16 (s, 3H); 2.48 (s, 3H); 2.58 (s, 3H); 2.94 (m, 1H); 4.03 (d, 1H); 4.25 (d, 1H); 4.37 (d, 1H); 4.70 (s, 1H); 5.00 (d, 1H); 5.73 (m, 2H); 6.28 (m, 1H); 6.32 (s, 1H); 6.40 (m, 1H); 7.11 (d, 1H); 7.30-7.65 (m); 7.75 (d, 2H); 8.15 (d, 2H).

PREPARATION 15A 2'-TES-Taxol 7-Triflate

A solution of 2'-triethylsilyltaxol [0.10 g; Chaudhary et al., *J. Org. Chem.* **1993**, *58*, 3798] and dry pyridine (0.29 mL) in CH₂Cl₂ (4 mL) is cooled to -20 °C and triflic anhydride (0.17 mL) is added. The solution is stirred and allowed to warm to about -10 °C. After 3 hours, saturated NH₄Cl is added to the reaction and the mixture is extracted with EtOAc. The organic extract solution is washed with dilute aqueous NaHSO₄, with saturated NaHCO₃, is dried over Na₂SO₄, filtered and concentrated at room temperature. The crude reaction product is chromatographed over silica gel (flash) using 30% EtOAc in hexane to elute the column and collecting fractions of 5 mL volume. The fractions (4-10) containing the desired product are combined and give the title compound (0.094 g).

PREPARATION 16A Baccatin III 7-O-triflate (24)

A solution of baccatin III (5.25 g, 8.93 mmols) in CH₂Cl₂ (21 mL) and pyridine (18.1 mL) is cooled in a -30 °C bath. Trifluoromethanesulfonic anhydride (3.76 mL, 6.31 g, 22.3 mmols) is added and the resulting mixture stirred and allowed to warm to room temperature over a period of an hour. The reaction is complete after 4 hrs; saturated aq NH₄Cl (50 mL) is added and the mixture extracted with CH₂Cl₂. The organic extract is washed successively with 1 M aq NaHSO₄ (50 mL), saturated aq NaHCO₃ (2 x 50 mL), saturated aq NaCl, and dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Care is taken not to warm the solution greater than 40 °C during removal of the solvent. A pale yellow solid is obtained and which is flash chromatographed over silica gel (6" silica gel in a 75 mm column, 125 mL fractions). The material is applied to the column in a CH₂Cl₂ solution and the column eluted with 5% CH₃CN-CH₂Cl₂. Fractions 19-35 contain the desired baccatin-III-7-O-triflate (4.837 g, 6.71 mmols, 75%) which is a white solid.

¹H NMR (CDCl₃, TMS) δ 8.10 (d, 2H, J = 7.2 Hz), 7.63 (t, 1H, J = 7.4 Hz), 7.49 (t, 2H, J = 7.6 Hz), 6.63 (s, 1H, H₁₀), 5.68 (d, 1H, J = 7.0 Hz, H₂), 5.52 (dd, 1H, J = 7.5, 10.1 Hz, H₇), 4.94 (d, 1H, J = 8.4 Hz, H₅), 4.86 (m, 1H, H₁₃), 4.35 (d, 1H, J = 8.4 Hz, H_{20a}), 4.15 (d, 1H, J = 8.4 Hz, H_{20b}), 4.01 (d, 1H, J = 7.0 Hz, H₃), 2.87 (5 lines, H_{14a}), 2.30 (s, 3H, -CH₃), 2.20 (s, 3H, -CH₃), 2.10-2.30 (m, H_{6a}, H_{6b}, H_{14b}), 1.87 (s, 3H, -CH₃), 1.59 (s, 3H, -CH₃), 1.19 (s, 3H, -CH₃), 1.05 (s, 3H, -CH₃).

PREPARATION 18A 7-Deoxy-7β,8β-methano-baccatin III (26)

A solution of 7-trifluoromethanesulfonyl-baccatin III (24, 87 mg, 0.12 mM) in distilled dioxane (1.5 mL) is treated with an aqueous sodium azide solution (0.10 g, 1.5 mM NaN₃ in 0.30 mL water.) The reaction is refluxed under nitrogen one hour. The mixture is diluted with ethyl acetate and washed with water and brine, dried over anhydrous sodium sulfate, and

evaporated. The product is purified by column chromatography on silica gel 60 in 25% ethyl acetate--methylene chloride giving a 56% yield (39 mg) of white crystalline 7-deoxy-7 β ,8 β -methano-baccatin III.

NMR (CDCl₃, TMS): δ 1.10 (s, 3H); 1.22 (s, 3H); 1.35 (m, 1H); 1.64 (m, 1H); 1.78 (s, 1H); 2.03 (s+m, 4H); 2.21 (s, 3H); 2.26 (s, 3H); 2.20-2.55 (m, 5H); 4.04 (d, 1H, J=8.5 Hz); 4.18 (d, 1H, J=7.5 Hz); 4.30 (d, 1H, J=8.5 Hz); 4.74 (d, 1H); 4.83 (m, 1H); 5.63 (d, 1H, J=7.5 Hz); 6.35 (s, 1H); 7.49 (m, 2H); 7.62 (m, 1H); 8.13 (m, 2H).

¹³C-NMR (CDCl₃, TMS): 15.15, 15.28, 20.43, 20.82, 21.99, 25.90, 26.35, 31.63, 35.19, 38.57, 38.76, 42.20, 67.51, 75.30, 76.20, 76.49, 79.23, 79.91, 84.73, 128.50, 129.33, 129.99, 132.59, 133.54, 144.19, 167.20, 169.63, 170.00, 202.08.

PREPARATION 19A 7-deoxy-7 α -azido-baccatin III (27)

A mixture of 7-trifluoromethanesulfonyl-baccatin III (24, 102 mg, 0.14 mM), sodium azide (13 mg, 0.20 mM), and 18-crown-6 (32 mg, 0.12 mM) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1.0 mL) is stirred at room temperature overnight under an inert atmosphere. The reaction is partitioned between ethyl acetate and water. The organic layer is dried over anhydrous sodium sulfate and evaporated. The crude product is purified by column chromatography on silica gel 60 in 15% ethyl acetate--methylene chloride. The product is further purified by crystallization from methylene chloride--hexane giving 37 mg of 7-deoxy-7 α -azido-baccatin III.

NMR (DMSO-d₆, TMS): δ 0.96 (s, 6H); 1.59 (s, 3H); 1.91(s, 3H); 2.13 (s, 3H); 2.25 (s, 3H); 2.10-2.35 (m, 4 H); 2.47 (m, 1H); 3.80 (m, 2H); 4.07 (d, 1H, J=8.0 Hz); 4.33 (d, 1H, J=8.0 Hz); 4.60 (s+m, 2H); 4.99 (dd, 1H); 5.35 (d, 1H); 5.48 (d, 1H, J=7.2 Hz); 6.79 (s, 1H); 7.59 (m, 2H); 7.69 (m, 1H); 8.05 (m, 2H).

¹³C-NMR (DMSO-d₆, TMS): 15.40, 17.31, 20.67, 22.20, 25.93, 29.81, 39.22, 40.63, 41.73, 55.57, 64.28, 65.91, 75.33, 76.91, 77.33, 78.22, 80.44, 80.94, 128.77, 129.58, 129.98, 130.28, 133.33, 145.43, 165.30, 168.75, 169.09, 207.11.

The following Examples further illustrate the subject invention.

Example 1 Preparation of:

2'-{[(2,2,2-Trichloroethyl)-oxy]carbonyl}-7-deoxy-7-fluorotaxol (Compound 13AA;IIIa), (([2aR[2 α ,4 α ,6 β ,9 α ,(α R*, β S*),11 α ,12 α ,12 α ,12 β]]- β -(Benzoylamino)- α -{[(2,2,2-trichloroethoxy)carbonyl]-oxy}benzenepropanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,-12,12a,12b-dodecahydro-4-fluoro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester)); and

2'-{[(2,2,2-Trichloroethyl)oxy]carbonyl}-7-deoxy-7 β ,8 β -methanotaxol (Compound

14AA), (((2aR-[2a α ,4 β ,4a β ,6 β ,9 α ,(α R*, β S*),11 α ,12 α ,12a α ,12b α)]- β -(Benzoylamino)- α -[[2,2,2-trichloroethoxy)-carbonyl]oxy]benzenepropanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9-,10,11,12,12a,12b-dodecahydro-11-hydroxy-8,13,13-trimethyl-5-oxo-4,4a;7,11-bismethano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester))

- 5 Dimethylaminosulfur trifluoride (methylDAST) (250 μ L, 0.340 g, 2.56 mmole) is added at once by syringe to a stirred and cooled (acetone-Dry Ice bath) solution of 2'-[(2,2,2-trichloroethyl)oxy]carbonyl]taxol 12AA [Magri, N. F.; Kingston, D. G. I. *J. Org. Chem.*, 1986, 51, 797] (1.60 g, 1.55 mmole) in CH_2Cl_2 (180 mL). The cooling bath is removed and the reaction container is allowed to come to room temperature. The reaction is stirred and starting material is found to
10 be completely consumed within 70 minutes judging from tlc evidence. The reaction is quenched by the addition of water and transferred to a separatory funnel with the aid of additional CH_2Cl_2 . The layers are separated and the organic layer is washed once with water, dried (Na_2SO_4), filtered, and concentrated to give a white solid (1.65 g). The residue is chromatographed over silica gel (40-63 μ m, 195 g in a 3.7 x 35 cm column; 40 mL fractions) using a CH_2Cl_2 solution for application
15 on the column and 25% acetone in hexane for elution of the column.

Fractions 32-39 contain a mixture of at least two compounds.

Fractions 40-42 contain a mixture which may include some of compound 14AA.

Fractions 43-49 (0.391 g) contain primarily compound 14AA (R_f = 0.22 in 30% acetone-hexane) together with two minor components.

- 20 Fractions 50-54 contain 0.162 g of a mixture of 14AA and 13AA. This mixture is rechromatographed over silica gel (Merck Lobar[®] size B column, 8 mL fractions) using CH_2Cl_2 for application to the column and 25% acetone-hexane for elution of the column. Fractions 58-70 contain 0.056 g of 14AA, which is combined (pool A) with the aforementioned 0.391 g from fractions 43-49 (total, 0.447 g), and fractions 76-92 contain 0.053 g of 13AA.

- 25 One of the two minor components of pool A is separated and is obtained as a pure compound by rechromatography of the mixture over silica gel (two Merck Lobar[®] size B columns, 9 mL fractions). The mixture is applied to the column in CH_2Cl_2 and the column is eluted with 25% EtOAc-hexane through fraction 72, 30% EtOAc-hexane through fraction 180, and with 40% EtOAc-hexane thereafter.

- 30 Fractions 195-215 (0.373 g) contain 14AA and the second minor component which is not separated until after removal of the troc protecting groups. Despite the presence of the minor component, compound 14AA forms beautiful crystals upon slow evaporation of the solvent and the following spectral data are recorded:

- 35 FAB mass spectrum gives peaks at 1012, 1010, 551, 533, 511, 491, 460, and 442 mass units;

¹H NMR (CDCl_3 , TMS) δ 8.19 (d, 2H, J = 7.1 Hz), 7.71 (d, 2H, J = 7.2 Hz), 7.59 (t, 1H),

-62-

7.48 (m), 7.36 (m), 6.98 (d, 1H, -NH-), 6.57 (s, 1H, H₁₀), 6.28 (t, 1H, J = 8.7 Hz, H₁₃), 6.08 (dd, 1H, J = 9.5, 2.7 Hz, H₃), 5.67 (d, 1H, J = 7.6 Hz, H₂), 5.54 (d, 1H, J = 2.8 Hz, H₂), 4.77 (dd, 2H, 2'-troc -CH₂-), 4.74 (1H, H₅), 4.32 (d, 1H, J = 8.6 Hz, H_{20a}), 4.09 (d, 1H, J = 8.6 Hz, H_{20b}), 4.07 (1H, H₃), 2.47 (s, 3H, -CH₃), 2.23 (dd, 1H, J_{H-7} = 9.9 Hz, J_{H-19a} = 5.3 Hz, H_{19b}), 2.19 (s, 3H, -CH₃), 1.90 (d, 3H, J = 1.3 Hz, -CH₃), 1.67 (dd, 1H, J_{H-7} = 7.2, J_{H-19a} = 5.3 Hz, H_{19b}), 1.38 (m, 1H, H₇), 1.26 (s, 3H, -CH₃), and 1.21 (s, 3H, -CH₃); ¹³C NMR (CDCl₃, TMS) 201.88, 169.64, 169.59, 167.45, 167.03, 166.96, 153.24, 140.41, 136.43, 133.89, 133.61, 133.36, 132.05, 130.31, 129.25, 129.15, 129.07, 128.95, 128.75, 128.68, 128.59, 127.17, 126.49, 93.82, 84.83, 80.11, 79.56, 79.47, 77.78, 77.23, 75.66, 75.41, 72.17, 52.58, 42.85, 38.57, 35.93, 35.04, 32.26, 26.05, 22.30, 21.60, 20.83, 15.82, 14.56 ppm.

Fractions 55-65 (0.480 g) contain pure compound **13AA** and when taken with the **13AA** obtained from the above rechromatography of mixed fractions, give **13AA** as a colorless crystalline solid:

R_f = 0.19 in 30% acetone-hexane;

FAB mass spectrum gives peaks at 1034, 1032, 1030, 571, 511, 460, 442, 210, and 105 mass units;

¹H NMR (CDCl₃, TMS) δ 8.18 (dd, 2H, J = 7.0, 1.5 Hz), 7.76 (dd, 2H, J = 7.0, 1.5 Hz), 7.62 (t, 1H), 7.50 (m), 7.43 (m), 6.95 (d, 1H, -NH-), 6.57 (s, 1H, H₁₀), 6.27 (t, 1H, H₁₃), 6.08 (dd, 1H, J = 9.5, 2.6 Hz, H₃), 5.78 (d, 1H, J = 7.3 Hz, H₂), 5.55 (d, 1H, J = 2.7 Hz, H₂), 5.05 (d, 1H, J = 7.5 Hz, H₅), 4.78 (d, 1H, J = 11.8 Hz, H_{20a}), 4.74 (d, 1H, J = 11.8 Hz, H_{20b}), 4.48 (dd, 1H, J_F = 48 Hz, H₇), 4.40 (d, 1H, J = 8.4 Hz, H_{20a}), 4.31 (d, 1H, J = 8.2 Hz, H_{20b}), 4.04 (d, 1H, 7.2 Hz, H₃), 2.63-2.45 (m), 2.49 (s, 3H), 2.27-2.10 (m), 2.20 (s, 3H), 1.91 (s, 3H), 1.74 (s, 3H), 1.20 (s, 3H), and 1.17 (s, 3H); ¹³C NMR (CDCl₃, TMS) 206.0, 169.9, 168.8, 167.2, 167.17, 153.2, 140.9, 136.4, 133.7, 133.5, 132.1, 130.3, 129.3, 129.2, 128.8, 128.7, 128.6, 127.2, 126.5, 96.2, 93.9, 81.9, 80.8, 78.8, 77.9, 77.8, 77.4, 77.2, 75.0, 72.1, 56.8 (d, J = 18 Hz), 52.7, 42.7, 40.1, 35.7, 33.9, 33.6, 25.8, 22.6, 21.3, 20.8, 14.6, 14.4 ppm.

Example 3 Preparation of:

N-Desbenzoyl-N-benzyloxycarbonyl-2'-[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7-fluorotaxol (**13BA**), (({2aR-[2α,4αβ,6β,9α,-(αR*,βS*),11α,12α,12α,12bα]}-β-(Benzyloxycarbonylamino)-α-[(2,2,2-trichloroethoxy)-carbonyl]oxy} benzenepropanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,-10,11,12,12a,12b-dodecahydro-4-fluoro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester)); and N-Desbenzoyl-N-benzyloxycarbonyl-2'-[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7β,8β-methanotaxol (**14BA**), (({2aR-[2α,4β,4aβ,6β,9α,-(αR*,βS*),-11α,12α,12α,12bα]}-β-(Benzyloxy-carbonylamino)-α-[(2,2,2-trichloroethoxy)carbonyl]oxy} benzenepropanoic acid,

6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,-12,12a,12b-dodecahydro-11-hydroxy-8,13,13-trimethyl-5-oxo-4,4a;7,11-bismethano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester));

The procedure described for the treatment of 2'-troc-taxol with methylDAST is followed (Example 1), using N-desbenzoyl-N-benzyloxycarbonyl-2'-troc-taxol (12BA, Preparation 6A; 0.223 g, 0.21 mmol) and dimethylaminosulfur trifluoride (methylDAST, 49 μ L, 0.066 g, 0.50 mmol total, added in two portions) in CH_2Cl_2 (20 mL) under N_2 at -78°C . Following workup, the crude reaction product mixture (0.211 g, white solid) is chromatographed over silica gel (40-63 μ m, two Merck size B columns) using a CH_2Cl_2 solution for application of the material to the column and 25% acetone-hexane for elution of the column. Fractions of 8 mL volume are collected. Fractions 107-118 contain a mixture of two components (0.065 g) which are separated in a second chromatography as described below. Fractions 128-140 contain compound 13BA (0.081 g, 0.076 mmol, 36%) which is characterized by the following spectral data:

^1H NMR (CDCl_3 , TMS) δ 8.16 (d, 2H, $J = 7.2$ Hz, aromatic), 7.63 (t, 1H, $J = 7.5$ Hz, aromatic), 7.53 (t, 2H, $J = 7.6$ Hz, aromatic), 7.30-7.45 (m, 5H, aromatic), 7.24 (m, aromatic), 7.12-7.19 (m, 2H, aromatic), 6.56 (s, 1H, H_{10}), 6.24 (t, 1H, H_{13}), 5.74 (d, 1H, $J = 7.4$ Hz, H_2), 5.74 (1H, -NH-), 5.62 (d, 1H, H_3), 5.44 (d, 1H, H_2), 5.09 (d, 1H, $J = 12.5$ Hz, PhCH_2HO -), 5.03 (d, 1H, H_5), 4.97 (d, 1H, PhCHH_bO -), 4.77 (d, 1H, $J = 11.9$ Hz, $-\text{OCH}_a\text{HCCl}_3$), 4.68 (d, 1H, $J = 11.9$ Hz, $-\text{OCHH}_b\text{CCl}_3$), 4.56 (dd, 1H, $J_F = 50$ Hz, H_7), 4.37 (d, 1H, H_{20a}), 4.30 (d, 1H, H_{20b}), 4.00 (d, 1H, $J = 7.3$ Hz, H_3), 2.57 (m, 1H, H_{6a}), 2.46 (s, 3H, $-\text{CH}_3$), 2.40 (m, 1H, H_{14a}), 2.21 (s, 3H, $-\text{CH}_3$), 2.15 (m, 1H, H_{14b}), 1.89 (s, 3H, $-\text{CH}_3$), 1.85 (m, 1H, H_{6b}), 1.74 (s, 3H, CH_3), 1.19 (s, 3H, $-\text{CH}_3$), 1.16 (s, 3H, $-\text{CH}_3$);

mass spectrum (FAB) 1060.2466, $\text{C}_{51}\text{H}_{53}\text{Cl}_3\text{FNO}_{16} + \text{H}$ requires 1060.2492, 571, 553, 511, 472, 389, 347, 329, 105, 91 m/z.

Pooled fractions 107-118 (0.065 g) from the preceding column are rechromatographed over silica gel (40-63 μ m, one Merck size B column) using CH_2Cl_2 for application to the column and 10% MeCN- CH_2Cl_2 for elution of the column. Fractions of 8 mL volume are collected.

Fractions 96-120 contain 0.043 g (0.041 mmol, 20%) of compound 14BA:

^1H NMR (CDCl_3 , TMS) δ 8.17 (d, 2H, $J = 7.1$ Hz, aromatic), 7.59 (t, 1H, aromatic), 7.52 (t, 2H, aromatic), 7.31-7.46 (m, 5H, aromatic), 7.24 (m, aromatic), 7.09 (m, 2H, aromatic), 6.32 (s, 1H, H_{10}), 6.28 (t, 1H, $J = 8.6$ Hz, H_{13}), 5.75 (d, 1H, $J = 10.0$ Hz, -NH-), 5.64 (d, 1H, $J = 7.8$ Hz, H_2), 5.59 (d, 1H, H_3), 5.41 (d, 1H, $J = 2.6$ Hz, H_2), 5.00 (d, 1H, $J = 12.5$ Hz, ArCH_aHO -), 4.91 (d, 1H, $J = 12.6$ Hz, ArCHH_bO -), 4.76 (d, 1H, $J = 9.8$ Hz, $-\text{OCH}_a\text{CCl}_3$), 4.73 (d, 1H, H_5), 4.68 (d, 1H, $J = 9.9$ Hz, $-\text{OCHH}_b\text{CCl}_3$), 4.30 (d, 1H, $J = 8.6$ Hz, H_{20a}), 4.07 (d, 1H, H_3), 4.05 (d, 1H, H_{20b}), 2.50 (m, 1H, H_{14a}), 2.43 (s, 3H, $-\text{CH}_3$), 2.36 (m, 1H, H_{6a}), 2.24 (m, 1H, H_{19a}), 2.20 (s, 3H, $-\text{CH}_3$), 2.10 (d, 1H, $J = 16.1$ Hz, H_{14b}), 1.88 (s, 3H, $-\text{CH}_3$), 1.66 (m, 1H, H_{19b}), 1.38 (m, 1H, H_7), 1.26 (s, 3H, $-\text{CH}_3$), 1.21 (s, 3H, $-\text{CH}_3$);

mass spectrum (FAB) 1040.2416, $C_{51}H_{52}Cl_3NO_{16} + H$ requires 1040.2430, 980, 962, 551, 491, 369, 105, 91 m/z.

Example 10 Preparation of [2aR-{2a α ,4a β ,6 β ,9 α ,(α R*, β S*),11 α ,12 α ,12a α ,12b α }}]- β -
 5 (Benzoylamino)- α -[[(2,2,2-trichloroethoxy)carbonyl]oxy]benzenepropanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4-fluoro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester;
 2'-[[(2,2,2-Trichloroethyl)oxy]carbonyl]-7-deoxy-7-fluorotaxol (Compound 13AA, IIIa)

A solution of 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]taxol [Magri, N. F.; Kingston, D. G.
 10 I. J. Org. Chem., 1986, 51, 797] (0.021 g, 0.020 mmole) in CH_2Cl_2 (1.5 mL) is added by syringe over a period of 5 min to a stirred and cooled (acetone-Dry Ice bath) solution of dimethylaminosulfur trifluoride (DAST) (2 μ L, 0.014 mmole) in CH_2Cl_2 (0.5 mL) contained in a 3 mL Reacti-vial[®]. The cooling bath is removed after 15 min and the reaction container is allowed to come to room temperature. The reaction is stirred and the solution is again cooled in an acetone-
 15 Dry Ice bath and more DAST (4 μ L, 0.028 mmole) in CH_2Cl_2 is added to the reaction. The cooling bath is removed after 15 min. and after 90 min. the reaction solution is diluted with additional CH_2Cl_2 and then is washed with water. The layers are separated and the organic layer is dried (Na_2SO_4), filtered, and concentrated to give a residue (0.017 g). The residue is chromatographed over silica gel (40-63 μ m, 60 g) using a CH_2Cl_2 solution for application on the column and 30%
 20 acetone in hexane for elution of the column to give the desired title product having a R_f = 0.19 (30% acetone-hexane):

FAB mass spectrum gives peaks at 1034, 1032, 1030, 571, 511, 460, 442, 210, and 105 mass units;

¹H NMR ($CDCl_3$, TMS) δ 8.18 (dd, 2H), 7.76 (dd, 2H), 7.62 (t, 1H), 7.50 (m), 7.43 (m),
 25 6.95 (d, 1H), 6.57 (s, 1H), 6.27 (t, 1H), 6.08 (dd, 1H), 5.78 (d, 1H), 5.55 (d, 1H), 5.05 (d, 1H), 4.78 and 4.76 (d, 2H), 4.66 (d, 0.5H), 4.50 (d, 0.5H), 4.40 (d, 1H), 4.31 (d, 1H), 4.04 (d, 1H), 2.63-2.45 (m), 2.49 (s, 3H), 2.27-2.10 (m), 2.20 (s, 3H), 1.91 (s, 3H), 1.74 (s, 3H), 1.20 (s, 3H), and 1.17 (s, 3H); ¹³C NMR ($CDCl_3$, TMS) 206.0, 169.9, 168.8, 167.2, 167.17, 153.2, 140.9, 136.4, 133.7, 133.5, 132.1, 130.3, 129.3, 129.2, 128.8, 128.7, 128.6, 127.2, 126.5, 96.2, 93.9, 81.9, 80.8, 78.8,
 30 77.9, 77.8, 77.4, 77.2, 75.0, 72.1, 56.8 d, J = 18Hz), 52.7, 42.7, 40.1, 35.7, 33.9, 33.6, 25.8, 22.6, 21.3, 20.8, 14.6, 14.4 ppm.

Example 11 Preparation of [2aR-{2a α ,4a β ,6 β ,9 α ,(α R*, β S*),11 α ,12 α ,12a α ,12b α }}]- β -
 (Benzoylamino)- α -hydroxybenzenepropanoic Acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-
 35 2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4-fluoro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-

7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester ; 7-Deoxy-7-fluorotaxol (Compound IIIb)

A solution of 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7-fluorotaxol (Compound 13AA, IIIa; 0.010g, 0.0097 mmole) in 9:1 methanol/acetic acid (1.0 mL) is stirred with activated
5 zinc metal (0.012 g) at room temperature. After 90 min, the reaction is worked up by removal of the zinc by filtration and concentration of the filtrate under reduced pressure. The residue is dissolved in CH₂Cl₂ and this solution is washed with 0.1N aq. HCl, with 5% aq. NaHCO₃, and with water. The aqueous layer is back extracted with CH₂Cl₂ and the combined organic extracts are dried (Na₂SO₄), filtered, and concentrated to give a residue (0.009 g). The residue is
10 chromatographed over silica gel (40-63 μm, 8mm x 250mm column) and is applied to the column in a CH₂Cl₂ solution. The column is eluted with 60 mL of 20% EtOAc in hexane and then is eluted with 40% EtOAc in hexane. The desired product (Compound IIIb) is obtained as a solid:

FAB mass spectrum 856, 571, 511, 286, 268, 240, 210, 105 mass units;

¹H NMR (CDCl₃, TMS) δ 8.15 (dd, 2H), 7.75 (dd, 2H), 7.63 (t, 1H), 7.50 (m), 7.38 (m),
15 7.06 (d, 1H), 6.53 (s, 1H), 6.18 (t, 1H), 5.83 (dd, 1H), 5.76 (d, 1H), 5.02 (d, 1H), 4.80 (t, 1H), 4.65 (d, 0.5H), 4.50 (d, 0.5H), 4.38 (d, 1H), 4.29 (d, 1H), 4.04 (d, 1H), 3.55 (d, 1H), 2.70-2.40 (m), 2.40 (s, 3H), 2.37-2.25 (m), 2.21 (s, 3H), 1.75 (3H), 1.62 (s, 3H), 1.20 (s, 3H), 1.18 (s, 3H); ¹³C NMR (CDCl₃, TMS) 205.7, 172.4, 169.5, 169.4, 167.1, 166.9, 140.4, 138.0, 133.8, 133.7, 132.4, 131.9, 130.2, 129.2, 129.0, 128.75, 128.71, 128.3, 127.02, 126.98, 81.9, 81.0, 78.6, 77.2, 74.8, 73.2, 72.1,
20 57.0 (J = 17 Hz), 54.7, 42.6, 39.9, 35.8, 16.0, 22.5, 21.0, 20.8, 14.7, 14.2 ppm.

Following the procedure described by Magri and Kingston for the preparation of 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]taxol, the 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl] derivative of 7-epitaxol (ref.: Ringel, I.; Horwitz, S. B. *J. Pharmacol. Exp. Ther.*, 1987, 242, 692; preferably Chaudhary et al., *J. Org. Chem.*, 1993, 58, 3798) is prepared.

25

Example 12 2'-[[(2,2,2-Trichloroethyl)oxy]carbonyl]-7-deoxy-7-epifluorotaxol

Following the procedure of Example 10, but substituting 2'-[[(2,2,2-trichloroethyl)-oxy]carbonyl]-7-epitaxol for 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-taxol, the title compound is prepared. The term 7-deoxy-7-epifluorotaxol as used in the name of the title compound means
30 only that the configuration of the fluorine substituent is epimeric to that of 2'-[[(2,2,2-Trichloroethyl)oxy]carbonyl]-7-deoxy-7-fluorotaxol (Compound 13AA, IIIa; Example 1) and does not imply a configuration analogous to that of 7-epitaxol.

Example 13 7-Deoxy-7-epifluorotaxol

35 Following the procedure of Example 11, but substituting 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7-epifluorotaxol for 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-

deoxy-7-fluorotaxol, the title compound is prepared. The term 7-deoxy-7-epifluorotaxol as used in the name of the title compound means only that the configuration of the fluorine substituent is epimeric to that of 7-deoxy-7-fluorotaxol (Compound IIb, Example 11) and does not imply a configuration analogous to that of 7-epitaxol.

5

Example 14 2'-[[(2,2,2-Trichloroethyl)oxy]carbonyl]taxol, 7-Methanesulfonate

Methanesulfonyl chloride (1.2 equivalents) is added dropwise to a solution of 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]taxol (1 equiv.) and pyridine (5 equiv.) in CH₂Cl₂ which is stirred at ice bath temperature. The reaction mixture is allowed to warm and stirring is continued until the evidence indicates that reaction is complete. The reaction mixture is quenched with ice water and is extracted with CH₂Cl₂ and these extracts are washed successively with dilute aqueous acid, dilute aqueous NaHCO₃, and water and then are dried, filtered, and concentrated to give the crude reaction product. Chromatography of the crude product over silica gel gives pure title compound.

15 **Example 15** 2'-[[(2,2,2-Trichloroethyl)oxy]carbonyl]-7-deoxy-7 α -chlorotaxol

A solution of 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]taxol, 7-methanesulfonate (1 equiv.) in N,N-dimethylformamide (DMF) is stirred with potassium chloride (10 equiv.). A phase transfer catalyst is added and the reaction mixture is warmed to increase the rate of reaction. The course of the reaction is followed by tlc. The reaction mixture is worked up by the addition of water and extraction with CH₂Cl₂. The organic extracts are dried, filtered, and concentrated and the crude reaction product residue is chromatographed over silica gel, yielding the pure title compound.

Example 16 7-Deoxy-7 α -chlorotaxol

Following the procedure of Example 11, but substituting 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7 α -chlorotaxol for 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7-fluorotaxol, the title compound is prepared.

Example 17 7-Deoxy-7 β -chlorotaxol

Following the procedures of Examples 14 and 15, but starting with 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-epitaxol, the title compound is prepared.

Following the general procedures of Examples 15 and 11 but using appropriate metal salts, such as sodium or potassium bromide and sodium or potassium iodide, in the procedure of Example 15, the following compounds are prepared:

7-Deoxy-7 α -bromotaxol;

35 7-Deoxy-7 β -bromotaxol;

7-Deoxy-7 α -iodotaxol;

7-Deoxy-7 β -iodotaxol.

Compounds of Formula III wherein X = chlorine, bromine or iodine can also prepared by reaction of an appropriately protected precursor (e.g., I wherein R₁ = -C₆H₅; R₂ = -NHC(O)C₆H₅; R₃ = H; R₄ = -OTROC; R₅ = H; R₁₀ = -COCH₃; and X = OH) with (C₆H₅)₃P/X₂; (C₆H₅)₃P/CX₄; or (C₆H₅O)₃P/X₂) following, for example, the numerous examples and experimental conditions described in Castro, B.R., Organic Reactions, 1983, 29, pp 1-162.

Derivatives of the 7-deoxy-7-halotaxols in which the 2'-hydroxyl group is esterified are prepared directly from the desired 7-deoxy-7-halotaxol by methods which are given in: Mathew, A. E., *et.al.*, *J. Med. Chem.*, 1992, *35*, 145; U.S. Patent 4,960,790; U.S. Patent 4,942,184; U.S. Patent 5,059,699.

Following the general procedures of Mathew et al. (see, e.g., U.S. Patent 4,960,790, 4,924,184 and 5,059,699) but substituting the appropriate 7-deoxy-7-halotaxol analog, the following compounds are prepared:

- 2'-succinyl-7-deoxy-7-fluorotaxol;
- 15 2'-(β -alanyl)-7-deoxy-7-fluorotaxolformate;
- 2'-glutaryl-7-deoxy-7-fluorotaxol;
- 2'-[-C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7-fluorotaxol;
- 2'-(β -sulfopropionyl)-7-deoxy-7-fluorotaxol;
- 2'-(2-sulfoethylamido)succinyl-7-deoxy-7-fluorotaxol;
- 20 2'-(3-sulfopropylamido)succinyl-7-deoxy-7-fluorotaxol;
- 2'-(triethylsilyl)-7-deoxy-7-fluorotaxol;
- 2'-(t-butyltrimethylsilyl)-7-deoxy-7-fluorotaxol;
- 2'-(N,N-diethylaminopropionyl)-7-deoxy-7-fluorotaxol;
- 2'-(N,N-dimethylglycyl)-7-deoxy-7-fluorotaxol;
- 25 2'-(glycyl)-7-deoxy-7-fluorotaxol;
- 2'-(L-alanyl)-7-deoxy-7-fluorotaxol;
- 2'-(L-leucyl)-7-deoxy-7-fluorotaxol;
- 2'-(L-isoleucyl)-7-deoxy-7-fluorotaxol;
- 2'-(L-valyl)-7-deoxy-7-fluorotaxol;
- 30 2'-(L-phenylalanyl)-7-deoxy-7-fluorotaxol;
- 2'-(L-prolyl)-7-deoxy-7-fluorotaxol;
- 2'-(L-lysyl)-7-deoxy-7-fluorotaxol;
- 2'-(L-glutamyl)-7-deoxy-7-fluorotaxol;
- 2'-(L-arginyl)-7-deoxy-7-fluorotaxol;
- 35 7-deoxy-7-fluorotaxotere;
- 2'-succinyl-7-deoxy-7-chlorotaxol;

- 2'-(β -alanyl)-7-deoxy-7-chlorotaxolformate;
 2'-glutaryl-7-deoxy-7-chlorotaxol;
 2'-[-C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7-chlorotaxol;
 2'-(β -sulfopropionyl)-7-deoxy-7-chlorotaxol;
 5 2'-(2-sulfoethylamido)succinyl-7-deoxy-7-chlorotaxol;
 2'-(3-sulfopropylamido)succinyl-7-deoxy-7-chlorotaxol;
 2'-(triethylsilyl)-7-deoxy-7-chlorotaxol;
 2'-(*t*-butyldimethylsilyl)-7-deoxy-7-chlorotaxol;
 2'-(*N,N*-diethylaminopropionyl)-7-deoxy-7-chlorotaxol;
 10 2'-(*N,N*-dimethylglycyl)-7-deoxy-7-chlorotaxol;
 2'-(glycyl)-7-deoxy-7-chlorotaxol;
 2'-(*L*-alanyl)-7-deoxy-7-chlorotaxol;
 2'-(*L*-leucyl)-7-deoxy-7-chlorotaxol;
 2'-(*L*-isoleucyl)-7-deoxy-7-chlorotaxol;
 15 2'-(*L*-valyl)-7-deoxy-7-chlorotaxol;
 2'-(*L*-phenylalanyl)-7-deoxy-7-chlorotaxol;
 2'-(*L*-proyl)-7-deoxy-7-chlorotaxol;
 2'-(*L*-lysyl)-7-deoxy-7-chlorotaxol;
 2'-(*L*-glutamyl)-7-deoxy-7-chlorotaxol;
 20 2'-(*L*-arginyl)-7-deoxy-7-chlorotaxol;
 7-deoxy-7-chlorotaxotere;
 2'-succinyl-7-deoxy-7-bromotaxol;
 2'-(β -alanyl)-7-deoxy-7-bromotaxolformate;
 2'-glutaryl-7-deoxy-7-bromotaxol;
 25 2'-[-C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7-bromotaxol;
 2'-(β -sulfopropionyl)-7-deoxy-7-bromotaxol;
 2'-(2-sulfoethylamido)succinyl-7-deoxy-7-bromotaxol;
 2'-(3-sulfopropylamido)succinyl-7-deoxy-7-bromotaxol;
 2'-(triethylsilyl)-7-deoxy-7-bromotaxol;
 30 2'-(*t*-butyldimethylsilyl)-7-deoxy-7-bromotaxol;
 2'-(*N,N*-diethylaminopropionyl)-7-deoxy-7-bromotaxol;
 2'-(*N,N*-dimethylglycyl)-7-deoxy-7-bromotaxol;
 2'-(glycyl)-7-deoxy-7-bromotaxol;
 2'-(*L*-alanyl)-7-deoxy-7-bromotaxol;
 35 2'-(*L*-leucyl)-7-deoxy-7-bromotaxol;
 2'-(*L*-isoleucyl)-7-deoxy-7-bromotaxol;

- 2'-(L-valyl)-7-deoxy-7-bromotaxol;
 2'-(L-phenylalanyl)-7-deoxy-7-bromotaxol;
 2'-(L-prolyl)-7-deoxy-7-bromotaxol;
 2'-(L-lysyl)-7-deoxy-7-bromotaxol;
 5 2'-(L-glutamyl)-7-deoxy-7-bromotaxol;
 2'-(L-arginyl)-7-deoxy-7-bromotaxol;
 7-deoxy-7-bromotaxotere;
 2'-succinyl-7-deoxy-7-iodotaxol;
 2'-(β-alanyl)-7-deoxy-7-iodotaxolformate;
 10 2'-glutaryl-7-deoxy-7-iodotaxol;
 2'-[C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7-iodotaxol;
 2'-(β-sulfopropionyl)-7-deoxy-7-iodotaxol;
 2'-(2-sulfoethylamido)succinyl-7-deoxy-7-iodotaxol;
 2'-(3-sulfopropylamido)succinyl-7-deoxy-7-iodotaxol;
 15 2'-(triethylsilyl)-7-deoxy-7-iodotaxol;
 2'-(t-butyl dimethylsilyl)-7-deoxy-7-iodotaxol;
 2'-(N,N-diethylaminopropionyl)-7-deoxy-7-iodotaxol;
 2'-(N,N-dimethylglycyl)-7-deoxy-7-iodotaxol;
 2'-(glycyl)-7-deoxy-7-iodotaxol;
 20 2'-(L-alanyl)-7-deoxy-7-iodotaxol;
 2'-(L-leucyl)-7-deoxy-7-iodotaxol;
 2'-(L-isoleucyl)-7-deoxy-7-iodotaxol;
 2'-(L-valyl)-7-deoxy-7-iodotaxol;
 2'-(L-phenylalanyl)-7-deoxy-7-iodotaxol;
 25 2'-(L-prolyl)-7-deoxy-7-iodotaxol;
 2'-(L-lysyl)-7-deoxy-7-iodotaxol;
 2'-(L-glutamyl)-7-deoxy-7-iodotaxol;
 2'-(L-arginyl)-7-deoxy-7-iodotaxol;
 7-deoxy-7-iodotaxotere; and
 30 pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic functional group.

Example 18 Preparation of {2a*R*-[2aα,4β,4aβ,6β,9α,(α*R*^{*},β*S*^{*}),11α,12α,12aα,12bα]}-β-(Benzoylamino)-α-[(2,2,2-trichloroethoxy)carbonyl]oxy} benzenepropionic acid,

- 35 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-8,13,13-trimethyl-5-oxo-4,4a;7,11-bismethano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester;

2'-{[(2,2,2-Trichloroethyl) oxy]carbonyl}-7-deoxy-7 β ,8 β -methanotaxol (Compound 14AA; IIa)

A solution of 2'-{[(2,2,2-trichloroethyl)oxy]carbonyl}taxol [Magri, N. F.; Kingston, D. G. I. *J. Org. Chem.*, 1986, 51, 797] (0.021 g, 0.020 mmole) in CH₂Cl₂ (1.5 mL) was added by syringe over a period of 5 min to a stirred and cooled (acetone-Dry Ice bath) solution of dimethylaminosulfur trifluoride (DAST) (2 μ L, 0.014 mole in CH₂Cl₂ (0.5 mL) contained in a 3 mL Reacti-vial®. The cooling bath was removed after 15 min and the reaction container was allowed to come to room temperature. The reaction was stirred and the solution was again cooled in an acetone-Dry Ice bath and more DAST (4 μ L, 0.028 mmole) in CH₂Cl₂ was added to the reaction. The cooling bath was removed after 15 min and after 90 min the reaction solution was diluted with additional CH₂Cl₂ and then was washed with water. The layers were separated and the organic layer was dried (Na₂SO₄), filtered, and concentrated to give a residue (0.017 g). The residue was chromatographed over silica gel (40-63 μ m, 60 g) using a CH₂Cl₂ solution for application to the column and 30% acetone in hexane for elution of the column. The desired title compound has R_f = 0.22 (30% acetone-hexane) and crystallizes from acetone-hexane as colorless needles:

FAB mass spectrum gives peaks at 1012, 1010, 551, 533, 511, 491, 460, and 442 mass units;

¹H NMR (CDCl₃, TMS) δ 8.19 (d, 2H), 7.71 (d, 2H), 7.59 (t, 1H), 7.48 (m), 7.36 (m), 6.98 (d, 1H), 6.57 (s, 1H), 6.28 (t, 1H), 6.08 (dd, 1H), 5.67 (d, 1H), 5.54 (d, 1H), 4.77 (dd, 2H), 4.74, 4.32 (d, 1H), 4.09 (d, 1H), 4.07, 2.47 (s, 3H), 2.19 (s, 3H), 1.90 (s, 3H), 1.67 (dd, 1H), 1.38 (m, 1H), 1.26 (s, 3H), and 1.21 (s, 3H); ¹³C NMR (CDCl₃, TMS) 201.88, 169.64, 169.59, 167.45, 167.03, 166.96, 153.24, 140.41, 136.43, 133.89, 133.61, 133.36, 132.05, 130.31, 129.25, 129.15, 129.07, 128.95, 128.75, 128.68, 128.59, 127.17, 126.49, 93.82, 84.83, 80.11, 79.56, 79.47, 77.78, 77.23, 75.66, 75.41, 72.17, 52.58, 42.85, 38.57, 35.93, 35.04, 32.26, 26.05, 22.30, 21.60, 20.83, 15.82, 14.56 ppm.

25

Example 19 Preparation of {2aR-[2a α ,4 β ,4a β ,6 β ,9 α ,(α R*, β S*)],11 α ,12 α ,12a α ,12b α]}- β -(Benzoylamino)- α -hydroxybenzenepropanoic Acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-8,13,13-trimethyl-5-oxo-4,4a;7,11-bismethano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester, 7-Deoxy-7 β ,8 β -methanotaxol (Compound IIb)

A solution of 2'-{[(2,2,2-trichloroethyl)oxy]carbonyl}-7-deoxy-7 β ,8 β -methanotaxol (Compound 14AA, IIa; 0.008 g, 0.0079 mmole) in 9:1 methanol/acetic acid (1.0 mL) was stirred with activated zinc metal (0.010 g) at room temperature. After 60 min, additional zinc (0.010 g) was added and stirring was continued for 30 min. Solids were removed from the reaction mixture by filtration and the filtrate was concentrated under reduced pressure. The residue so obtained was dissolved in CH₂Cl₂ and the solution was washed successively with aqueous 0.1 N HCl, with

aqueous 5% NaHCO₃, and with water. The organic layer was dried (Na₂SO₄), filtered, and concentrated and the residue was chromatographed over silica gel (40-63 μm, 8 x 250 mm column, applied in CH₂Cl₂ solution and eluted with 40% ethyl acetate in hexane). The title compound is a colorless solid:

- 5 FAB mass spectrum gives peaks at 836, 776, 758, 551, 533, 491, 286, 240, and 105 mass units;

¹H NMR (CDCl₃, TMS) δ 8.19 (d, 2H), 7.69 (d, 2H), 7.60 (t, 1H), 7.60-7.35 (m), 6.95 (d, 1H), 6.31 (s, 1H), 6.25 (t, 1H), 5.82 (d, 1H), 5.66 (d, 1H), 4.78 (dd, 1H), 4.72 (d, 1H), 4.31 (d, 1H), 4.07 (d, 1H), 4.06 (m, 1H), 2.40 (s, 3H), 2.20 (s, 3H), 1.60 (s, 3H), 1.38 (m, 1H), 1.26 (s, 3H), and
10 1.22 (s, 3H); ¹³C NMR (CDCl₃, TMS) 204.45, 201.81, 172.74, 169.87, 169.56, 167.41, 166.96, 140.12, 138.04, 134.07, 133.53, 131.93, 130.33, 129.28, 129.04, 128.74, 128.55, 128.32, 127.04, 126.86, 84.86, 80.03, 79.57, 79.40, 77.21, 75.66, 75.46, 73.22, 72.28, 54.79, 42.86, 38.54, 36.07, 35.09, 32.15, 26.11, 22.27, 21.49, 20.88, 15.77, and 14.59 ppm.

- 15 **Example 20** Preparation of 2'-[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7β,8β-methano-taxol (14AA; IIa) from 2'-[(2,2,2-Trichloroethyl)-oxy]carbonyl]-7-deoxy-7-aminotaxol

An ice-cold solution of sodium nitrite (1.5 equivalents) is added in portions to a vigorously stirred, ice-cold two phase mixture of a solution of 2'-[(2,2,2-Trichloroethyl)-oxy]carbonyl]-7-deoxy-7-aminotaxol (1 equivalent) in ether and a solution of sulfuric acid in water. The mixture
20 is stirred at ice-bath temperature for several hours following the addition. Then, excess nitrous acid is quenched by the addition of an aqueous solution of urea. The aqueous phase of the mixture is brought to near neutral pH by the careful addition of sodium carbonate, the layers are separated, and the aqueous phase is further extracted with additional ether. The combined ether extracts are dried, filtered, and concentrated to give the crude reaction product. Chromatography of the crude
25 product over silica gel gives pure compound 14AA.

- Example 21** Preparation of 2'-[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7β,8β-methano-taxol (14AA, IIa) from 2'-[(2,2,2-Trichloroethyl)-oxy]carbonyl]taxol 7-Trifluoromethyl-sulfonate

A solution of 2'-[(2,2,2-Trichloroethyl)-oxy]carbonyl]taxol 7-Trifluoromethylsulfonate in
30 80% ethanol-water is warmed and the reaction is followed by tlc techniques. When complete, the reaction solution is neutralized with sodium bicarbonate, excess ethanol is removed under reduced pressure, and the aqueous phase is extracted with methylene chloride. The extracts are dried, filtered, and concentrated to give the crude reaction product. The crude product is chromatographed over silica gel to give pure compound 14AA.

Example 22 N-Debenzoyl-N-benzyloxycarbonyl-7-deoxy-7-fluorotaxol (Compound 18): (({2aR-[2a α ,4a β ,6 β ,9 α ,(α R*, β S*),11 α ,12 α ,12a α ,12b α]}- β -(Benzyloxycarbonylamino)- α -hydroxybenzene-propanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4-fluoro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester))

Following the general procedure of Example No. 11 [reaction of 2'-trac-7-deoxy-7-fluorotaxol with activated zinc], but using N-debenzoyl-N-benzyloxycarbonyl-2'-[[{(2,2,2-trichloroethyl)oxy]carbonyl}-7-deoxy-7-fluorotaxol (Example 3, Compound 13BA; 0.079 g, 0.074 mmol) and activated zinc metal (0.153 g) in CH₃OH-HOAc (9:1, 16 mL) and EtOAc (8 mL) the desired product 18 is prepared. Following workup (two hrs reaction time) and chromatography (silica gel, 40% EtOAc-hexane, 8 mL fractions) of the crude product is obtained and the desired product 18 is eluted in fractions 59-76 as a solid and characterized on the basis of the following analytical data:

¹H NMR (CDCl₃, TMS) δ 8.14 (d, 2H, J = 7.4 Hz), 7.62 (t, 1H, J = 7.4 Hz), 7.52 (t, 2H, J = 7.75, 7.30 Hz), 7.30-7.42 (m, 5H), 7.17 (m, 2H), 6.53 (s, 1H, H₁₀), 6.18 (t, 1H, H₁₃), 5.75 (d, 1H, -NH-), 5.73 (d, 1H, J = 7.2 Hz, H₂), 5.38 (d, 1H, H₃), 5.09 (d, 1H, J = 12.5 Hz, -OCH₂HPh), 4.99 (d, 1H, H₅), 4.96 (d, 1H, J = 12.3 Hz, -OCHH_bPh), 4.66 (d, 1H, H₂), 4.57 (dd, 1H, J_F = 54 Hz, H₇), 4.36 (d, 1H, J = 8.4 Hz, H_{20a}), 4.29 (d, 1H, H_{20b}), 3.41 (d, 1H, J = 7.3 Hz, H₃), 2.63-2.46 (7 lines, 1H), 2.38 (s, 3H, -CH₃), 2.43-2.30 (m, 1H), 2.28-2.10 (m, 1H), 2.22 (s, 3H, -CH₃), 2.01 (m, 1H), 1.77 (s, 3H, -CH₃), 1.73 (s, 3H, -CH₃), 1.19 (s, 3H, -CH₃), 1.16 (s, 3H, -CH₃);

¹³C NMR (CDCl₃, TMS), 206, 172, 169.5, 169.3, 166.9, 156, 140.5, 138, 137, 133.7, 132, 130.2, 129.3, 128.8, 128.7, 128.4, 128.0, 127.6, 126.7, 96, 93, 81.9, 80.9, 78.6, 78, 74.8, 73.6, 71.8, 66.8, 57, 56, 42.5, 39.9, 35.9, 34, 34, 25.9, 22.4, 21.0, 20.8, 14.5, 14 ppm;

mass spectrum 886, 571, 511, 371, 347, 329, 316, 298, 105, 91 m/z.

25

Example 23 N-Debenzoyl-N-benzyloxycarbonyl-7-deoxy-7 β ,8 β -methanotaxol (Compound 21): (({2aR-[2a α ,4 β ,4a β ,6 β ,9 α ,(α R*, β S*),11 α ,12 α ,12a α ,12b α]}- β -(Benzyloxycarbonylamino)- α -hydroxybenzenepropanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-8,13,13-trimethyl-5-oxo-4,4a,7,11-bismethano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester))

Following the general procedure of Example 11 [reaction of 2'-trac-7-deoxy-7-fluorotaxol with activated zinc], but using N-debenzoyl-N-benzyloxycarbonyl-2'-[[{(2,2,2-trichloroethyl)oxy]carbonyl}-7-deoxy-7 β ,8 β -methanotaxol (14BA; 0.040 g, 0.038 mmol) and activated zinc metal (0.072 g followed by an additional 0.072 g) in CH₃OH-HOAc (9:1, 10 mL) the desired product 21 is prepared. Following workup after 3 hrs reaction time and chromatography (silica gel, 40% EtOAc-hexane, 8 mL fractions) of the crude product, starting material (0.007 g) is

35

recovered in fractions 30-37 and the desired product (**21**, 0.020 g, 0.023 mmol, 61%) is eluted in fractions 75-100 and obtained as a solid and characterized on the basis of the following analytical data:

¹H NMR (CDCl₃, TMS) δ 8.17 (d, 2H, J = 7.3 Hz), 7.58 (m, 1H), 7.50 (t, 2H), 7.42-7.30 (m, 5H), 7.24 (m), 7.08 (m, 2H), 6.31 (s, 1H, H₁₀), 6.26 (t, 1H, J = 8.6 Hz, H₁₃), 5.70 (d, 1H, J = 9.6 Hz, -NH-), 5.64 (d, 1H, J = 7.7 Hz, H₂), 5.38 (d, 1H, J = 8.1 Hz, H₃), 4.98 (d, 1H, J = 12.5 Hz, -OCH₂HPh), 4.88 (d, 1H, J = 12.5 Hz, -OCHH₂Ph), 4.71 (d, 1H, J = 3.7 Hz, H₅), 4.65 (s, 1H, H₂), 4.28 (d, 1H, J = 8.6 Hz, H_{20a}), 4.07 (d, 1H, H₃), 4.05 (d, 1H, H_{20b}), 2.49-2.34 (m, 1H), 2.38 (s, 3H, -CH₃), 2.23 (m), 2.21 (s, 3H, -CH₃), 2.08 (m), 1.94 (m), 1.82 (s, 3H, -CH₃), 1.37 (m, 1H, H₇), 1.25 (s, 3H, -CH₃), 1.21 (s, 3H, -CH₃);

¹³C NMR (CDCl₃, TMS) 202, 172.5, 169.2, 169.1, 167, 155.5, 149.5, 138, 136, 133.5, 133, 130.0, 128.6, 128.4, 128.1, 127.7, 127.2, 126.3, 84.5, 79.9, 79.2, 79.0, 75.3, 75.2, 73, 71.7, 66.5, 56, 42.5, 38.2, 36, 34.7, 32, 25.7, 21.5, 21, 20.5, 15.5, 14.2 ppm;

mass spectrum: 866.3423, C₄₈H₅₁NO₁₄ + H requires 866.3388, 848, 806, 788, 551, 533, 491, 105, 91 m/z.

Example 24 N-Debenzoyl-N-(*t*-butyl)oxycarbonyl-2'-[[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7-fluorotaxol (Compound **13DA**); (({2aR-[2α,4α,6β,9α,(αR*,βS*),11α,12α,12a,12bα]}-β-[(*t*-Butyl)oxycarbonylamino]-α-[[[(2,2,2-trichloroethoxy)carbonyl]oxy]benzenepropanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4-fluoro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester)); and N-Debenzoyl-N-(*t*-butyl)oxycarbonyl-2'-[[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7β,8β-methanotaxol (Compound **14DA**), (({2aR-[2α,4β,4aβ,6β,9α,(αR*,βS*),11α,12α,12a,12bα]}-β-[(*t*-Butyl)oxycarbonylamino]-α-[[[(2,2,2-trichloroethoxy)carbonyl]oxy]benzenepropanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-8,13,13-trimethyl-5-oxo-4,4a,7,11-bismethano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester));

The general procedure of Example 10 [reaction of 2'-troc-taxol with methylDAST] is followed, using N-debenzoyl-N-(*t*-butyl)oxycarbonyl-2'-troc-taxol (Compound **12DA**; 1.800 g, 1.75 mmols) and dimethylaminosulfur trifluoride (methylDAST, 286 μL, 0.390 g, 2.93 mmols) in CH₂Cl₂ (120 mL) under N₂ at -78°C. Following workup, the crude product mixture (1.77 g) is chromatographed over silica gel (40-63 μm, 191 g in a 37 x 350 mm column, 45 mL fractions) using a CH₂Cl₂ solution for application of the material to the column and 20% acetone-hexane (1.5 L) followed by 25 % acetone-hexane to elute the column. A mixture containing **14DA** (0.511 g) is eluted in fractions 41-46. Fractions 47-48 (0.085 g) contain a mixture of products. Fractions 49-61 (0.814 g) contain pure **13DA**. Rechromatography of the mixed fractions 47-48 provides

additional amounts of a mixture containing 14DA and of pure 13DA.

Pure 13DA is obtained as a solid and characterized on the basis of the following analytical data:

¹H NMR (CDCl₃, TMS) δ 8.15 (d, 2H, J = 7.2 Hz), 7.62 (t, 1H, J = 7.2 Hz), 7.51 (t, 2H, J = 7.7 Hz), 7.25-7.44 (m, 5H), 6.58 (s, 1H, H₁₀), 6.28 (t, 1H, J = 8.7 Hz, H₁₃), 5.77 (d, 1H, J = 7.2 Hz, H₂), 5.51 (d, 1H, -NH-), 5.48 (d, 1H, J = 10.0 Hz, H₃), 5.40 (d, 1H, J = 2.0 Hz, H₂), 5.05 (d, 1H, J = 8.1 Hz, H₅), 4.77 (d, 1H, J = 11.8 Hz, troc-H_a), 4.68 (d, 1H, J = 11.8 Hz, troc-H_b), 4.58 (dd, 1H, J = 4.6, 46.9 Hz, H₇), 4.39 (d, 1H, J = 8.4 Hz, H_{20a}), 4.27 (d, 1H, J = 8.4 Hz, H_{20b}), 4.04 (d, 1H, J = 7.1 Hz, H₃), 2.57 (m, 1H, H_{6a}), 2.48 (s, 3H, -CH₃), 2.21 (s, 3H, -CH₃), 1.91 (s, 3H, -CH₃), 1.73 (s, 3H, -CH₃), 1.34 (s, 9H, Me₃C-), 1.23 (s, 3H, -CH₃), 1.17 (s, 3H, -CH₃);

mass spectrum, found: 1026.2660, C₄₈H₅₅Cl₃FNO₁₆ + H requires 1026.2648, 970, 571, 511, 407, 389, 347, 329, 105, 57 m/z.

All fractions containing a mixture of 14DA are combined and rechromatographed over silica gel (two size B Merck Lobar columns, 9 mL fractions) by applying the material to the column in a CH₂Cl₂ solution and eluting the column with 10% CH₃CN-CH₂Cl₂ (68 fractions) followed by 15% CH₃CN-CH₂Cl₂.

The pure compound 14DA is eluted in fractions 100-131 as a solid and characterized on the basis of the following analytical data:

¹H NMR (CDCl₃, TMS) δ 8.15 (d, 2H, J = 7.1 Hz), 7.61 (t, 1H, J = 7.3 Hz), 7.51 (t, 2H, J = 7.5 Hz), 7.30-7.44 (m, 5H), 6.34 (s, 1H, H₁₀), 6.30 (t, 1H, J = 8.6 Hz, H₁₃), 5.67 (d, 1H, J = 7.6 Hz, H₂), 5.54 (d, 1H, -NH-), 5.45 (d, 1H, J = 10.1 Hz, H₃), 5.38 (d, 1H, J = 2.3 Hz, H₂), 4.76 (d, 1H, J = 11.8 Hz, troc-H_a), 4.76 (1H, H₅), 4.69 (d, 1H, J = 11.8 Hz, troc-H_b), 4.33 (d, 1H, J = 8.6 Hz, H_{20a}), 4.09 (d, 1H, J = 7.5 Hz, H₃), 4.04 (d, 1H, J = 8.7 Hz, H_{20b}), 2.48 (m, 1H, H_{14a}), 2.44 (s, 3H, -CH₃), 2.37 (m, 1H, H_{6a}), 2.24 (m, 1H, H_{19a}), 2.20 (s, 3H, -CH₃), 2.11 (d, 1H, J = 16.0 Hz, H_{14b}), 1.90 (s, 3H, -CH₃), 1.66 (m, 1H, H_{19b}), 1.37 (m, 1H, H₇), 1.28 (s, 9H, Me₃C-), 1.27 (s, 3H, -CH₃), 1.25 (s, 3H, -CH₃);

mass spectrum, found: 1006.2560, C₄₈H₅₄Cl₃NO₁₆ + H requires 1006.2486, 950, 551, 533, 491, 369, 327, 105, 57 m/e.

Example 25 N-Debenzoyl-N-(*t*-butyl)oxycarbonyl-7-deoxy-7-fluorotaxol (Compound 20), (({2aR-[2α,4α,6β,9α,(αR*,βS*),11α,12α,12α,12βα]}-β-[(*t*-Butyl)oxycarbonylamino]-α-hydroxybenzene-propanoic acid, 6,12b-Bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4-fluoro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]-oxet-9-yl Ester)),

The general procedure of Example 11 [reaction of 2'-troc-7-deoxy-7-fluorotaxol with activated zinc] is followed, using N-debenzoyl-N-(*t*-butyl)oxycarbonyl-2'-[(2,2,2-

-75-

trichloroethyl)oxy]carbonyl}-7-deoxy-7-fluorotaxol (13DA, 0.100 g, 0.097 mmol) and activated zinc metal (0.183 g followed by an additional 0.050 g) in CH₃OH-HOAc (9:1, 10 mL). After 1 hr of reaction time, the reaction mixture is stored overnight at -33°C, then worked up and the crude product chromatographed (silica gel, 40% EtOAc-hexane, 8 mL fractions) to give the desired product 20 in fractions 53-76 as a solid and characterized on the basis of the following analytical data:

¹H NMR (CDCl₃, TMS) δ 8.13 (d, 2H, J = 7.2 Hz), 7.62 (t, 1H, J = 7.4 Hz), 7.51 (t, 2H, J = 7.5 Hz), 7.30-7.42 (m, 5H), 6.56 (s, 1H, H₁₀), 6.21 (t, 1H, H₁₃), 5.76 (d, 1H, J = 7.2 Hz, H₂), 5.42 (d, 1H, J = 9.7 Hz, -NH-), 5.29 (d, 1H, H₃), 5.01 (d, 1H, J = 7.5 Hz, H₅), 4.63 (m, 1H, H₂), 4.57 (dd, 1H, J = 4.3, 46.8 Hz, H₇), 4.37 (d, 1H, J = 8.4 Hz, H_{20a}), 4.27 (d, 1H, J = 8.4 Hz, H_{20b}), 4.04 (d, 1H, J = 7.1 Hz, H₃), 2.56 (seven lines, 1H, H_{6a}), 2.39 (s, 3H, -CH₃), 2.31 (m, 1H), 2.25 (m, 1H), 2.22 (s, 3H, -CH₃), 2.14 (dd, 1H), 1.81 (s, 3H, -CH₃), 1.73 (s, 3H, -CH₃), 1.34 (s, 9H, Me₃C-), 1.23 (s, 3H, -CH₃), 1.18 (s, 3H, -CH₃);

Example 26 N-Debenzoyl-N-(*t*-butyl)oxycarbonyl-7-deoxy-7β,8β-methanotaxol (Compound 23), (({2*aR*-[2*αα*,4*β*,4*αβ*,6*β*,9*α*,(*αR*^{*},*βS*^{*}),11*α*,12*α*,12*αα*,12*βα*]}-β-[(*t*-Butyl)oxycarbonylamino]-*α*-hydroxybenzenepropanoic acid, 6,12*b*-Bis(acetyloxy)-12-(benzoyloxy)-2*a*,3,4,4*a*,5,6,9,10,11,12,12*a*,12*b*-dodecahydro-11-hydroxy-8,13,13-trimethyl-5-oxo-4,4*a*;7,11-bismethano-1*H*-cyclodeca[3,4]benz[1,2-*b*]-oxet-9-yl Ester))

The general procedure of Example 11 [reaction of 2'-trac-7-deoxy-7-fluorotaxol with activated zinc] is followed, using N-debenzoyl-N-(*t*-butyl)oxycarbonyl-2'-[[{(2,2,2-trichloroethyl)oxy]carbonyl}-7-deoxy-7β,8β-methanotaxol (14DA, 0.100 g, 0.099 mmol) and activated zinc metal (0.200 g followed by an additional 0.050 g) in CH₃OH-HOAc (9:1, 10 mL). Following workup after 3 hrs reaction time and chromatography (silica gel, 40% EtOAc-hexane, 8 mL fractions) of the crude product there is obtained, the desired product 23 which is eluted in fractions 58-86 a solid and is characterized on the basis of the following analytical data:

¹H NMR (CDCl₃, TMS) δ 8.15 (d, 2H, J = 7.2 Hz), 7.61 (t, 1H, J = 7.3 Hz), 7.51 (t, 2H, J = 7.7 Hz), 7.28-7.45 (m, 5H), 6.33 (s, 1H, H₁₀), 6.27 (t, 1H, H₁₃), 5.67 (d, 1H, J = 7.6 Hz, H₂), 5.36 (d, 1H, J = 9.5 Hz, H₃), 5.30 (m, 1H, -NH-), 4.73 (d, 1H, J = 3.7 Hz, H₂), 4.62 (m, 1H, H₅), 4.31 (d, 1H, J = 8.6 Hz, H_{20a}), 4.09 (d, 1H, J = 7.5 Hz, H₃), 4.04 (d, 1H, J = 8.7 Hz, H_{20b}), 2.46 (d of t, 1H, J = 4.3, 16.1 Hz, H_{6a}), 2.38 (s, 3H, -CH₃), 2.24 (m, 1H), 2.21 (s, 3H, -CH₃), 2.10 (d, 1H, J = 16.0 Hz), 1.85 (s, 3H, -CH₃), 1.67 (dd, 1H, J = 7.1, 5.2 Hz), 1.36 (m, 1H, H₇), 1.28 (s, 12 H, Me₃C-, CH₃-), 1.25 (s, 3H, -CH₃);

Example 29 2'-TES-7-deoxy-7*α*-chlorotaxol

A solution of 2'-TES-taxol 7-triflate (Preparation 15A; 1 equiv.) in N,N-dimethylformamide

(DMF) is stirred with potassium chloride (10 equiv.). A phase transfer catalyst is added and the reaction mixture is warmed to increase the rate of reaction. The course of the reaction is followed by tlc. The reaction mixture is worked up by the addition of water and extraction with CH_2Cl_2 . The organic extracts are dried, filtered, and concentrated and the crude reaction product residue is chromatographed over silica gel, yielding the pure title compound.

Example 30 7-Deoxy-7 α -chlorotaxol

Following the procedures of Preparation 12A, but starting with 2'-TES-7-deoxy-7 α -chlorotaxol, the title compound is prepared.

Following the general procedures of Example 29 and 30 but using appropriate metal salts, such as sodium or potassium bromide and sodium or potassium iodide, in the procedure of Example 29, the following compounds are prepared:

7-Deoxy-7 α -bromotaxol;

7-Deoxy-7 β -bromotaxol;

7-Deoxy-7 α -iodotaxol;

7-Deoxy-7 β -iodotaxol.

Example 31: Preparation of N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7-fluoro-taxol; Compound 28

N-Debenzoyl-N-Cbz-7-deoxy-7-fluoro-taxol 18 (60 mg, 0.07 mM; Preparation 39) is dissolved in 3 mL absolute ethanol and 20 mg 10% Pd on carbon is added. This is hydrogenated at atmospheric pressure for 6 hrs. TLC shows no starting material left so reaction is filtered through Celite and concentrated in vacuo. The residue, which is 13-(β -phenyl-isoseriny)-7-fluoro-baccatin III, (19, 52 mg, 0.07 mM; Preparation 40) is dissolved in 700 μL THF and cooled to 0°C and 7 μL (0.061mM) *t*-butyl isocyanate added. TLC shows some amine remaining so another 7 μL is added. After 20 hrs the solution is concentrated in vacuo and chromatographed over 6 gm of silica gel packed in 1:2 EtOAc:hexane. The column is eluted with 30 mL 1:2 EtOAc:Hexane, 60 mL 2:3 EtOAc:hexane, 50 mL 1:1 EtOAc:hexane, and 20 mL 2:1 EtOAc:hexane collecting 3 mL fractions. The desired N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7-fluoro-taxol is found in fractions 35-52.

Mass Spec (FAB-High Res.) Theory: 851.3766 Found: 851.3792

^1H NMR (CDCl_3 ; TMS): δ 1.16 (s,3H); 1.20 (s); 1.72 (s,3H); 1.80 (s,3H); 2.15-2.60 (m); 2.19 (s,3H); 2.52 (s,3H); 4.02 (d,1H); 4.28 (d,1H); 4.35 (d,1H); 4.55 (dd,1H); 4.59 (d,1H); 4.88 (br s,1H); 4.99 (d,1H); 5.34 (m,2H); 5.76 (d,1H); 6.13 (m,1H); 6.55 (s,1H); 7.32 (m); 7.49 (m,2H); 7.61 (m,1H); 8.11 (d,2H)

Example 32: Preparation of N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7 β ,8 β -methano-taxol;
Compound 29

N-Debenzoyl-N-Cbz-7-deoxy-7 β ,8 β -methano-taxol 21 (60 mg, 0.07 mM; Preparation 42) is dissolved in 3 mL absolute ethanol and 20 mg 10% Pd on carbon is added. This is hydrogenated
5 at atmospheric pressure for 5.5 hrs. TLC shows no starting material left so reaction is filtered through Celite and concentrated in vacuo.

The residue, which is 13-(β -phenyl-isoserinyl)-7-deoxy-7 β ,8 β -methano-baccatin III, (22, 52 mg, 0.07 mM; Preparation 43) is dissolved in 1 mL THF and 8 mL (0.07mM) *t*-butyl isocyanate added. TLC shows some amine remains so the reaction is cooled to 0°C and 7 mL *t*-butyl
10 isocyanate added. Amine still remains so another 7 mL and 3x 5mL is added checking the reaction by TLC between each addition. To the reaction is added water to quench and the solution is partitioned between acidic brine and EtOAc. The layers are separated and the organic layer is filtered through Na₂SO₄ and concentrated in vacuo and chromatographed over 6 gm of silica gel packed in 1:2 EtOAc:hexane. The column is eluted with 30 mL 1:2 EtOAc:hexane, 50mL 2:3
15 EtOAc:hexane, and 80 mL 1:1 EtOAc:hexane collecting 3 mL fractions. The desired N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7 β ,8 β -methano-taxol is found in fractions 29-48.

Mass Spec (FAB-High Res.) Theory: 831.3704 Found: 831.3717

¹H NMR (CDCl₃; TMS): δ 1.18 (s); 1.23 (s,3H); 1.26 (s,3H); 1.66 (m); 1.82 (s,3H); 1.98-2.48 (m); 2.20 (s,3H); 2.38 (s,3H); 4.05 (m,2H); 4.30 (d,1H); 4.50 (m,1H); 4.60 (d,1H); 4.73
20 (m,1H); 5.33 (m,1H); 5.66 (d,1H); 6.19 (m,1H); 6.31 (s,1H); 7.32 (m); 7.51 (m,2H); 7.61 (m,1H); 8.13 (d,2H)

Derivatives of the 7-deoxy-7 β ,8 β -methano-taxols in which the 2'-hydroxyl group is esterified are prepared directly from the desired 7-deoxy-7 β ,7 β -methano-taxol by methods which are given in: Mathew, A. E., *et.al.*, *J. Med. Chem.*, 1992, 35, 145; U.S. Patent 4,960,790; U.S. Patent
25 4,942,184; U.S. Patent 5,059,699.

Following the general procedures of Mathew et al. (see, e.g., U.S. Patent 4,960,790, 4,924,184 and 5,059,699) but substituting the appropriate 7-deoxy-7 β ,8 β -methano-taxol analog, the following compounds are prepared:

- 2'-succinyl-7-deoxy-7 β ,8 β -methano-taxol;
- 30 2'-(β -alanyl)-7-deoxy-7 β ,8 β -methano-taxolformate;
- 2'-glutaryl-7-deoxy-7 β ,8 β -methano-taxol;
- 2'-[-C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7 β ,8 β -methano-taxol;
- 2'-(β -sulfopropionyl)-7-deoxy-7 β ,8 β -methano-taxol;
- 2'-(2-sulfoethylamido)succinyl-7-deoxy-7 β ,8 β -methano-taxol;
- 35 2'-(3-sulfopropylamido)succinyl-7-deoxy-7 β ,8 β -methano-taxol;
- 2'-(triethylsilyl)-7-deoxy-7 β ,8 β -methano-taxol;

-78-

- 2'-(t-butyltrimethylsilyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(N,N-diethylaminopropionyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(N,N-dimethylglycyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(glycyl)-7-deoxy-7 β ,8 β -methano-taxol;
5 2'-(L-alanyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(L-leucyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(L-isoleucyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(L-valyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(L-phenylalanyl)-7-deoxy-7 β ,8 β -methano-taxol;
10 2'-(L-prolyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(L-lysyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(L-glutamyl)-7-deoxy-7 β ,8 β -methano-taxol;
2'-(L-arginyl)-7-deoxy-7 β ,8 β -methano-taxol;
7-deoxy-7 β ,8 β -methano-taxotere; and
15 pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic functional group.

Taxol and the other starting taxol analogs are known or can be readily prepared by known methods. See The Chemistry of Taxol, Pharmac. Ther., Vol 52, pp 1-34, 1991 as well as:

- 20 U.S. Patent Nos. 4,814,470; 4,857,653; 4,942,184; 4,924,011; 4,924,012; 4,960,790;
5,015,744; 5,059,699; 5,136,060; 5,157,049; 4,876,399; 5,227,400 as well as PCT
Publication No. WO 92/09589, European Patent Application 90305845.1 (Publication No.
A2 0 400 971), 89400935.6 (Publication No. A1 0 366 841) and 90402333.0 (Publication
No. 0 414 610 A1), 87401669.4 (A1 0 253 739), 92308608.6 (A1 0 534 708), 92308609.4
(A1 534 709), and PCT Publication Nos. WO 91/17977, WO 91/17976, WO 91/13066,
25 WO 91/13053 all of which are incorporated herein by reference.

- The compounds of the invention can be formulated per se in pharmaceutical preparations or formulated in the form of pharmaceutically acceptable salts thereof, particularly as nontoxic pharmaceutically acceptable addition salts or acceptable basic salts. These salts can be prepared from those compounds of the invention which contain acidic or basic groups according to
30 conventional chemical methods.

- Normally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess thereof of the desired salt forming inorganic or organic acid in a suitable solvent or various combination of solvents. As an example, the free base can be dissolved in an aqueous solution of the appropriate acid and the salt recovered by standard techniques, for example,
35 by evaporation of the solution. Alternatively, the free base can be dissolved in an organic solvent such as a lower alkanoyl, an ether, an alkyl ester, or mixtures thereof, for example, methanol,

ethanol, ether, ethylacetate, an ethylacetate-ether solution, and the like, whereafter it is treated with the appropriate acid to form the corresponding salt. The salt is recovered by standard recovery techniques, for example, by filtration of the desired salt on spontaneous separation from the solution or it can be precipitated by the addition of a solvent in which the salt is insoluble and recovered therefrom.

The taxol derivatives of the invention can be utilized in the treatment of cancers, due to their cytotoxic, antitumor activity. The new compounds are administrable in the form of tablets, pills, powder mixtures, capsules, injectables, solutions, suppositories, emulsions, dispersions, food premix, and in other suitable form. The pharmaceutical preparation which contains the compound is conveniently admixed with a nontoxic pharmaceutical organic carrier or a nontoxic pharmaceutical inorganic carrier, usually about 0.01 mg up to 2500 mg, or higher per dosage unit, preferably 50-500 mg. Typical of pharmaceutically acceptable carriers are, for example, mannitol, urea, dextrans, lactose, potato and maize starches, magnesium stearate, talc, vegetable oils, polyalkylene glycols, ethyl cellulose, poly(vinylpyrrolidone), calcium carbonate, ethyl oleate, isopropyl myristate, benzyl benzoate, sodium carbonate, gelatin, potassium carbonate, silicic acid, and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain nontoxic auxiliary substances such as emulsifying, preserving, wetting agents, and the like as for example, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene monostearate, glyceryl tripalmitate, dioctyl sodium sulfosuccinate, and the like.

Exemplary of a typical method for preparing a tablet containing the active agents is to first mix the agent with a nontoxic binder such as gelatin, acacia mucilage, ethyl cellulose, or the like. The mixing is suitably carried out in a standard V-blender and usually under anhydrous conditions. Next, the just prepared mixture can be slugged through conventional tablet machines and the slugs fabricated into tablets. The freshly prepared tablets can be coated, or they can be left uncoated. Representative of suitable coatings are the nontoxic coatings including shellac, methylcellulose, carnauba wax, styrene-maleic acid copolymers, and the like. For oral administration, compressed tablets containing 0.01 milligram, 5 milligrams, 25 milligrams, 50 milligrams, 500 milligrams, etc., up to 2500 milligrams are manufactured in the light of the above disclosure and by art known fabrication techniques well known to the art and set forth in Remington's Pharmaceutical Science, Chapter 39, Mack Publishing Co., 1965.

To formulate the tablet, the active compound, cornstarch, lactose, dicalcium phosphate and calcium carbonate are uniformly blended under dry conditions in a conventional V-blender until all the ingredients are uniformly mixed together. Next, the cornstarch paste is prepared as a 10% paste and it is blended with the just prepared mixture until a uniform mixture is obtained. The mixture is then passed through a standard light mesh screen, dried in an anhydrous atmosphere and then blended with calcium stearate, and compressed into tablets, and coated if desired. Other tablets

containing 10, 50, 100, 150 mgs, etc., are prepared in a like fashion.

The following Formulation I is an example of a tablet formulation comprising a compound of the invention.

5

<u>FORMULATION I</u>	
Ingredients:	Per tablet, mg.
Active compound	50.0
Cornstarch	15.0
10 Cornstarch paste	4.5
Calcium carbonate	15.0
Lactose	67.0
Calcium stearate	2.0
15 Dicalcium phosphate	50.0

15

The manufacture of capsules containing 10 milligrams to 2500 milligrams for oral use consists essentially of mixing the active compound with a nontoxic carrier and enclosing the mixture in a polymeric sheath, usually gelatin or the like. The capsules can be in the art known soft form of a capsule made by enclosing the compound in intimate dispersion within an edible, compatible carrier, or the capsule can be a hard capsule consisting essentially of the novel compound mixed with a nontoxic solid such as talc, calcium stearate, calcium carbonate, or the like. Capsules containing 25 mg, 75 mg, 125 mg, and the like, of the novel compound, singularly or mixtures of two or more of the novel compounds are prepared, for example, as follows:

25

<u>FORMULATION II</u>	
Ingredients	Per Capsule, mg.
Active compound	50.0
Calcium carbonate	100.0
30 Lactose, U.S.P.	200.0
Starch	130.0
Magnesium stearate	4.5

30

The above ingredients are blended together in a standard blender and then discharged into commercially available capsules. When higher concentrations of the active agent is used, a corresponding reduction is made in the amount of lactose.

35

The compounds of the invention can also be freeze dried and, if desired, combined with other pharmaceutically acceptable excipients to prepare formulations suitable for parenteral, injectable administration. For such administration, the formulation can be reconstituted in water (normal, saline), or a mixture of water and an organic solvent, such as propylene glycol, ethanol, and the like.

The dose administered, whether a single dose, multiple dose, or a daily dose, will of course, vary with the particular compound of the invention employed because of the varying potency of the compound, the chosen route of administration, the size of the recipient and the nature of the patient's condition. The dosage administered is not subject to definite bounds, but it will usually be an effective amount, or the equivalent on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active drug to achieve its desired pharmacological and physiological effects.

Typically the compounds of the invention can be administered by intravenous injection at doses of 1-500 mg per patient per course of treatment, preferable with doses of 2-100 mg, the exact dosage being dependent on the age, weight, and condition of the patient. An example of a suitable formulation for injection is using a solution of the compound of the invention in a mixture of polysorbate alcohol and dehydrated alcohol (e.g., 1:1) followed by dilution with 5% dextrose in water prior to infusion or injection.

The compounds of Formula I (including II and III) are useful for the same cancers for which taxol has been shown active, including human ovarian tumors, mammary tumors, and malignant melanoma, lung tumors, gastric tumors, colon tumors, head and neck tumors, and leukemia. See, e.g., the clinical pharmacology of taxol is reviewed by Eric K. Rowinsky and Ross C. Donehower, *The Clinical Pharmacology and Use of Antimicrotubule Agents in Cancer Chemotherapeutics*, Pharmac. Ther., Vol 52, pp 35-84, 1991. Clinical and preclinical studies with taxol are reviewed by William J. Slichenmyer and Daniel D. Von Hoff, *Taxol: A New and Effective Anti-cancer Drug*, Anti-Cancer Drugs, Vol. 2, pp 519-530, 1991.

The biological activity of the 7-deoxy-7 β ,8 β -methanotaxol compounds (Formula II) of the invention has been confirmed using well known procedures. For example, comparison of the cytotoxicity of 7-deoxy-7 β ,8 β -methano-taxol (Compound IIb; product of example 19) with taxol itself in L1210 mouse leukemia carcinoma cells in culture indicated that the IC₉₀ (90% growth inhibitory concentration) for 7-deoxy-7 β ,8 β -methanotaxol was 0.025 micrograms/ml and for taxol was 0.06 micrograms/ml. In an *in vitro* tubulin polymerization assay, conducted after the manner of F. Gaskin, et al., *J. Mol. Biol.*, 89:737, 1974, 7-deoxy-7 β ,8 β -methano-taxol was able to induce tubulin polymerization *in vitro* at 20°C in a manner very similar to taxol.

The biological activity of the 7-deoxy-7-halotaxol compounds (Formula III) of the invention has been confirmed using well known procedures. For example, comparison of the

-82-

cytotoxicity of 7-deoxy-7-fluorotaxol (Compound IIIb; product of example 11) with taxol itself in A2780 (human ovarian carcinoma) cells in culture indicated that the IC₉₀ (90% growth inhibitory concentration) for 7-deoxy-7-fluorotaxol was 0.016 micrograms/ml and for taxol was 0.007 micrograms/ml. In an *in vitro* tubulin polymerization assay, conducted after the manner of F. Gaskin, et al., J. Mol. Biol., 89:737, 1974, 7-deoxy-7-fluorotaxol was able to induce tubulin polymerization *in vitro* at 20°C in a manner very similar to taxol. In this assay, 7-deoxy-7-fluoro taxol was approximately half as potent as taxol.

The biological activity of the compounds of this invention has been further confirmed using well known procedures against L1210 leukemia and the results set forth in Table I. The results were obtained using standard well known procedure (Li, L.H.; Kuentzel, S.L.; Murch, L.L.; Pschigoga, L.M.; and W.C. Krueger, "Comparative biological and biochemical effects of nogalamycin and its analogs on L1210 leukemia," Cancer Res. 39:4816-4822 (1979)). The results are expressed as an IC₅₀ which is the drug concentration required to inhibit cell proliferation to 50% of that of untreated control cells. Lower numbers indicated greater activity.

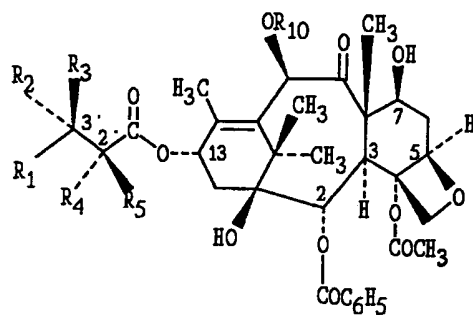
15

TABLE I

	<u>Compound No.</u>	<u>L1210 (IC₅₀ μg/ml)</u>
5	13AA	0.054
	14AA	> 0.1
	IIIb	0.010
10	IIb	0.012
	13DA	0.015
	14DA	0.012
15	20	0.0038
	23	0.0046
	28	0.0055
	29	0.006
20	Taxol	0.015
	Taxotere	0.004

-84-

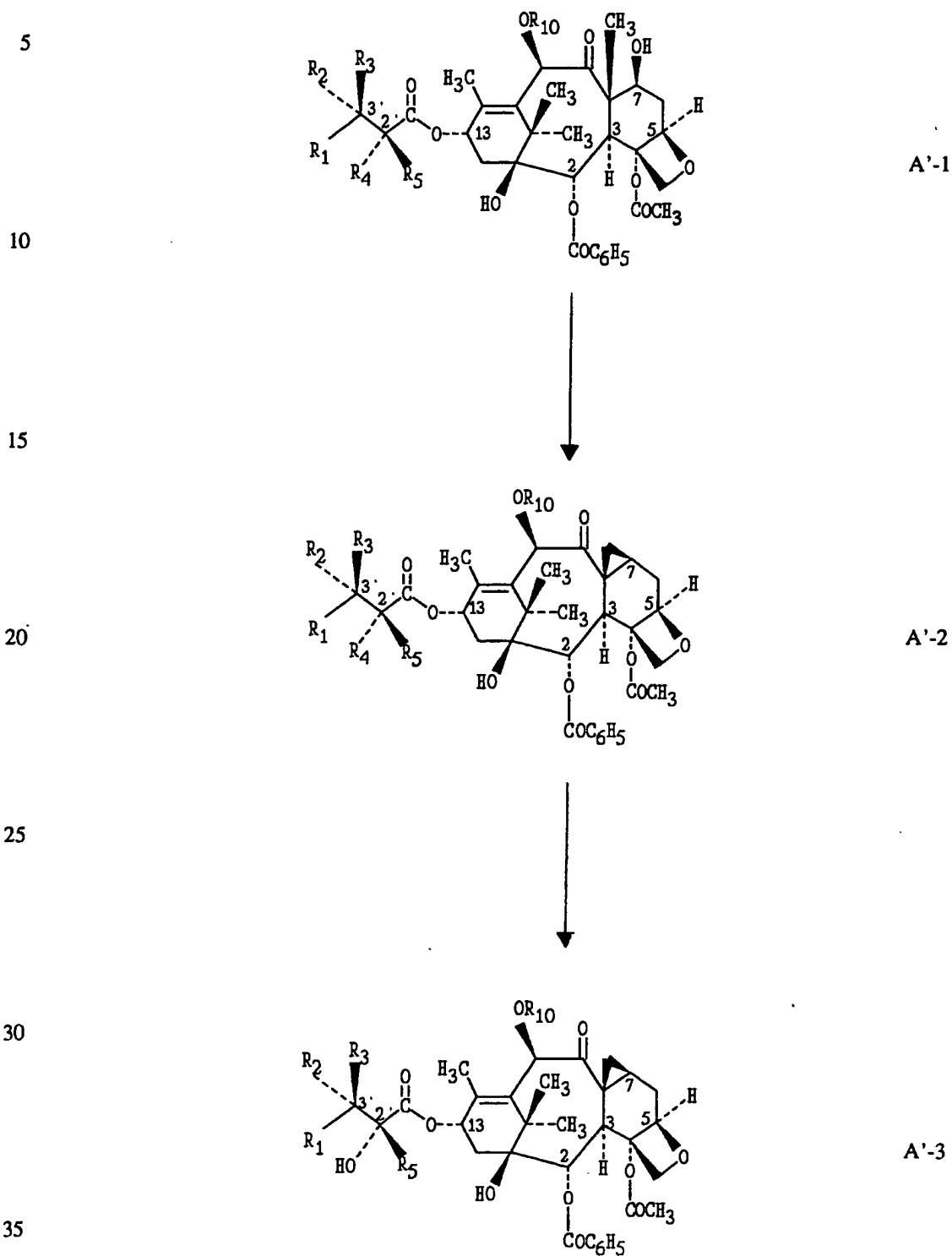
CHART A-I



A-1

-85-

CHART A-II



-86-

CHART A-III

5

10

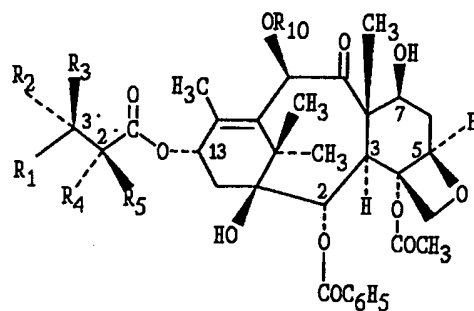
15

20

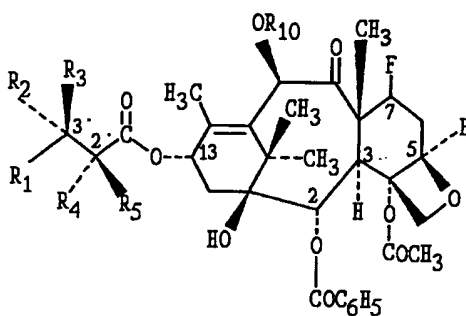
25

30

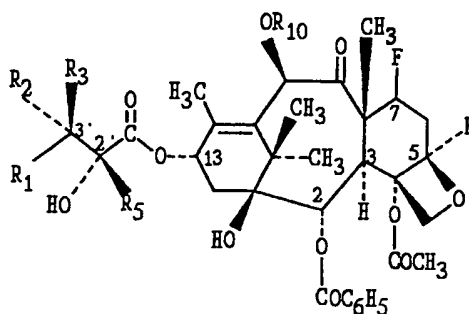
35



A''-1



A''-2



A''-3

CHART A'

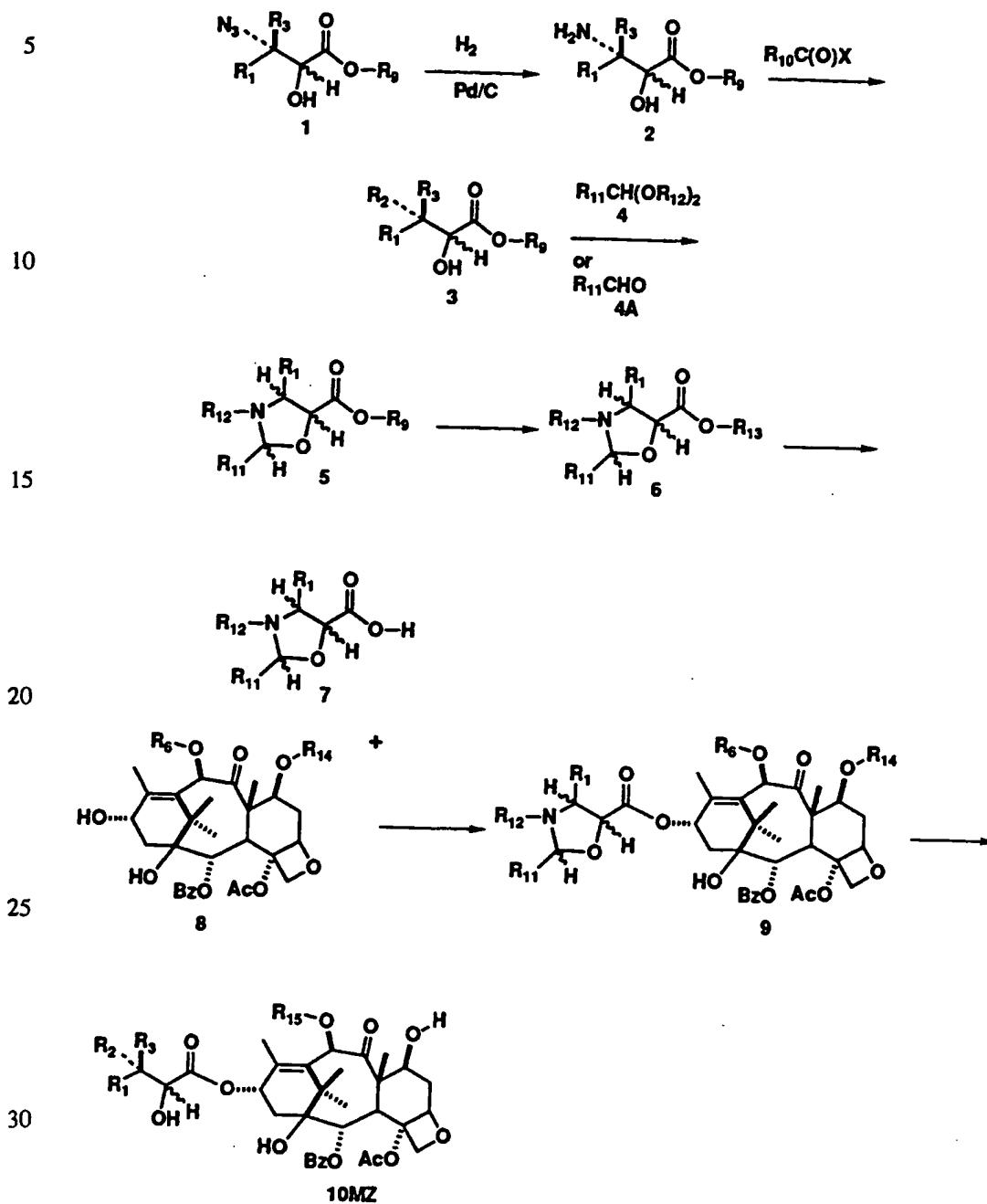
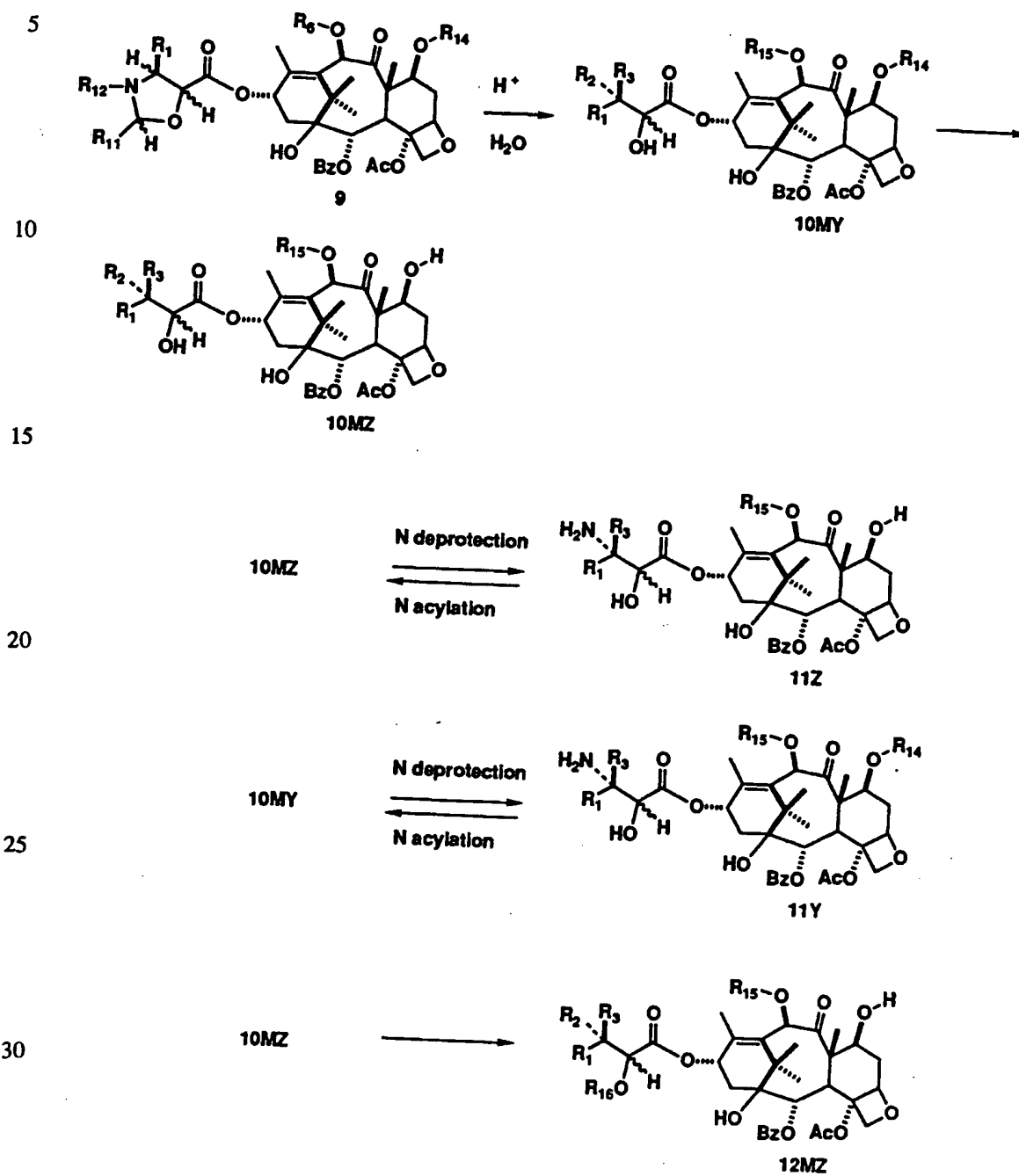
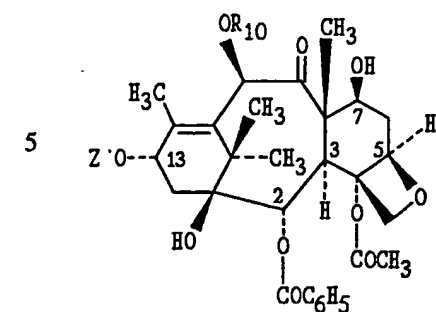


CHART B



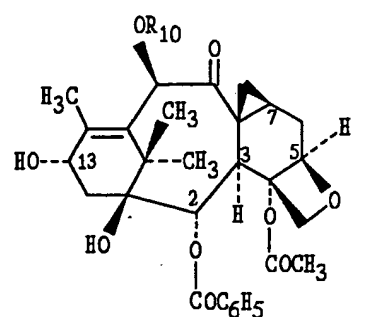
-89-

CHART B-II



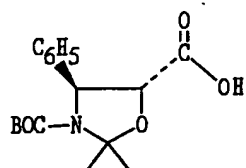
10

15



B-2

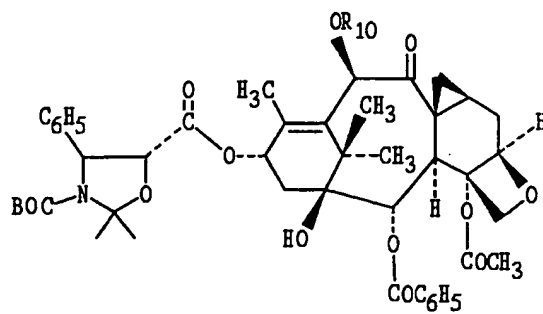
20



B-3

25

30



B-4

35

-90-

CHART B-III

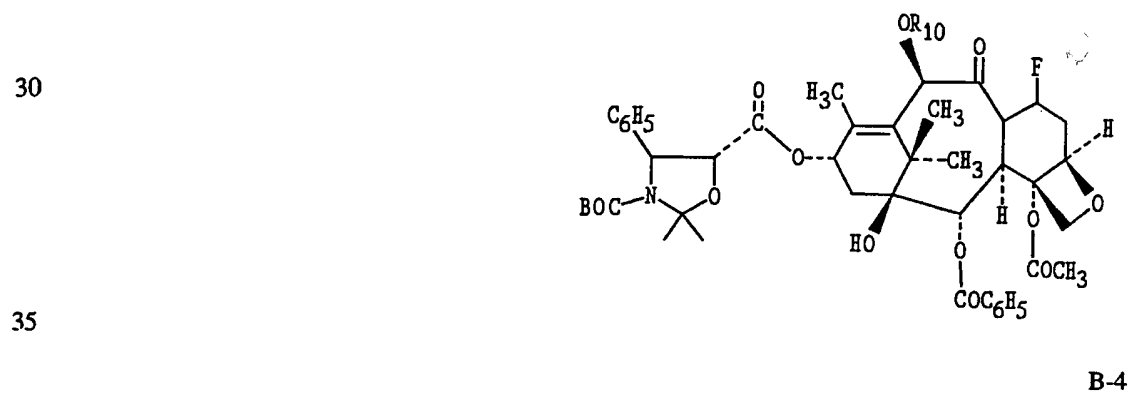
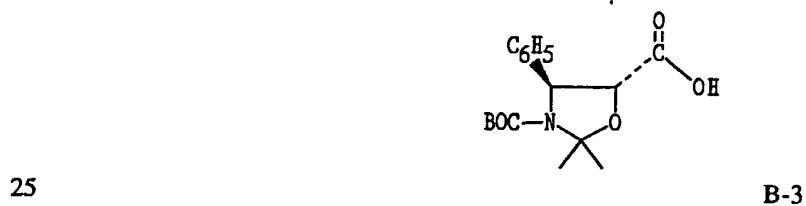
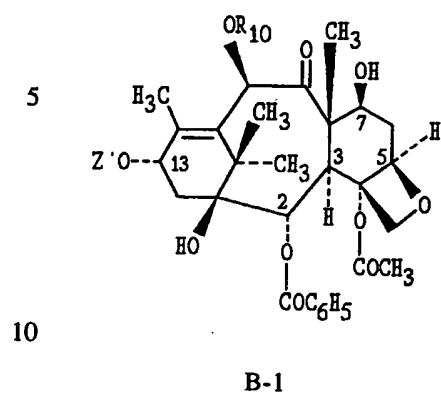
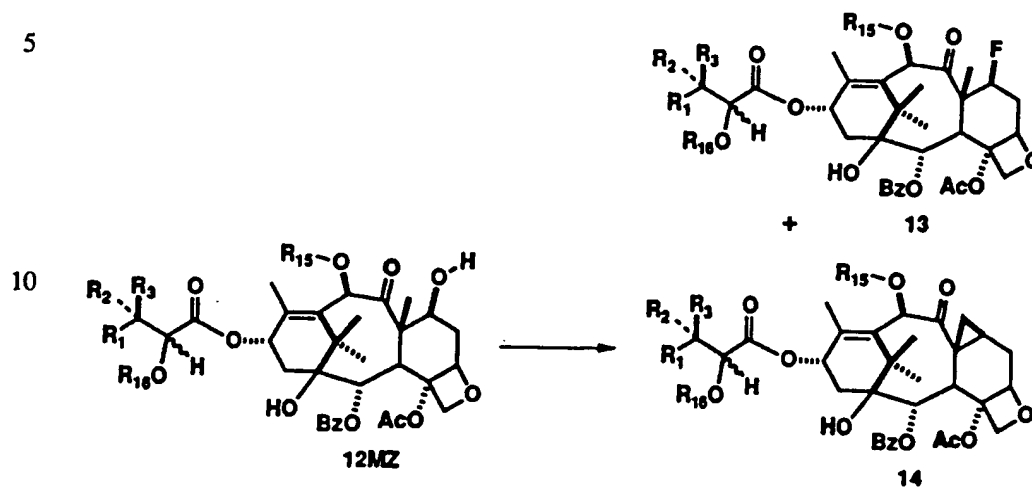
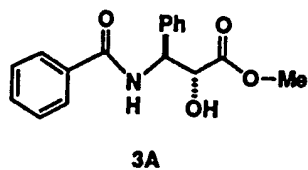
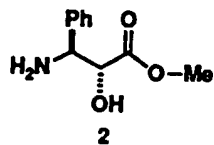
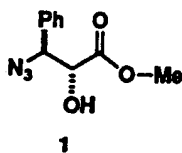


CHART C

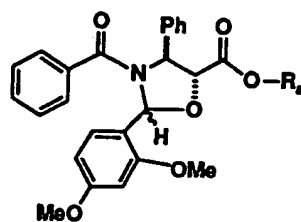
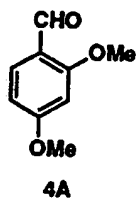
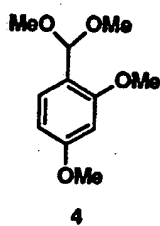


FORMULA CHART

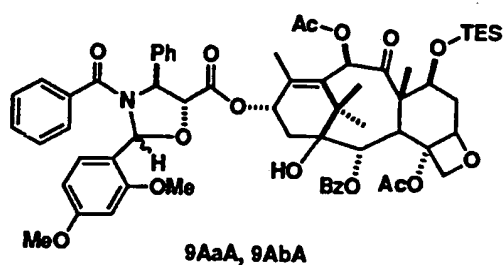
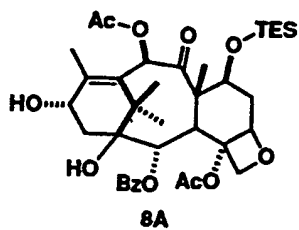
5



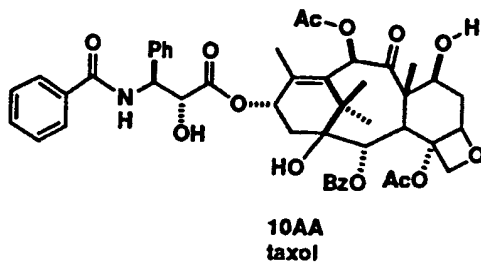
10



15



25



TES = Si(Et)₃
Ph = phenyl
Ac = C(O)CH₃
Bz = C(O)Ph

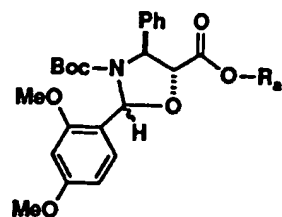
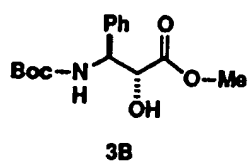
30

35

FORMULA CHART
cont.

5

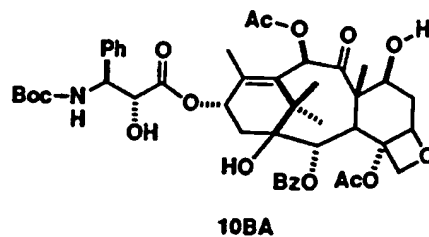
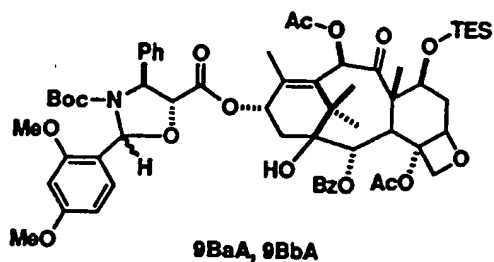
10



5Ba, 5Bb $R_2 = \text{Me}$
6Ba, 6Bb $R_2 = \text{K}$
7Ba, 7Bb $R_2 = \text{H}$

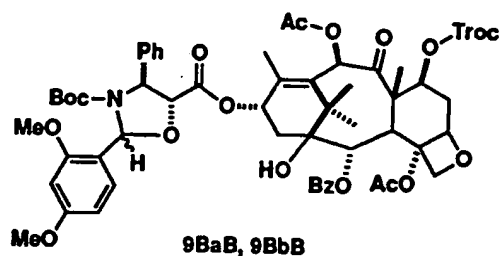
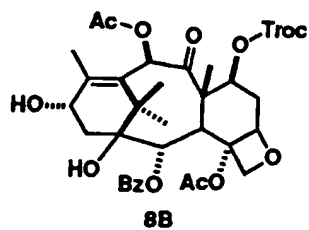
15

20



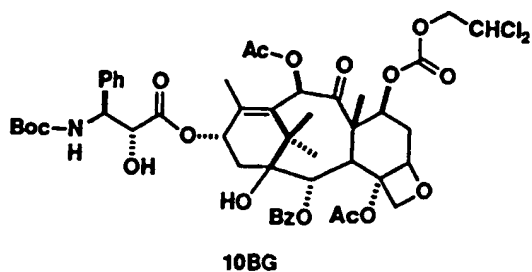
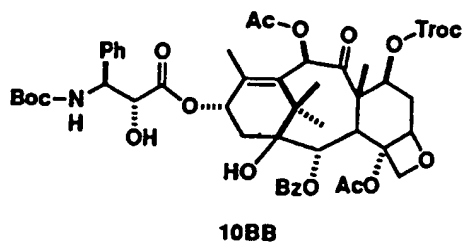
25

30



35

40



45

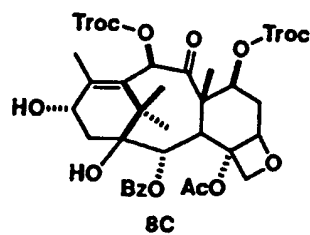
Troc = $\text{C}(\text{O})\text{OCH}_2\text{CCl}_3$
Boc = $\text{C}(\text{O})\text{O}-t\text{-Bu}$

50

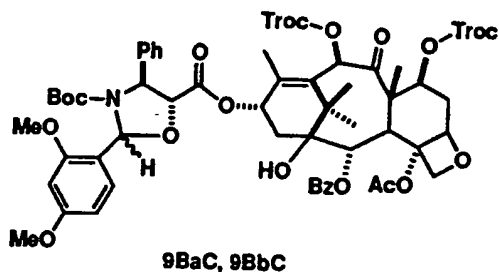
FORMULA CHART
cont.

5

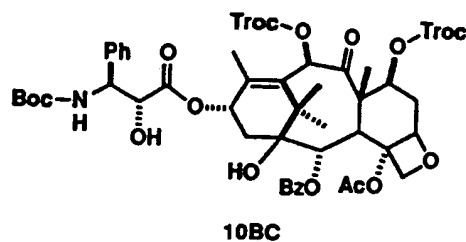
10



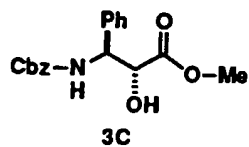
15



20

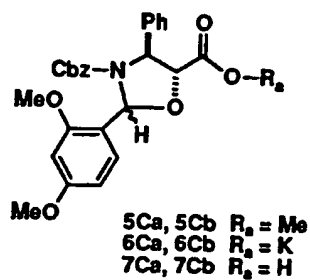


25

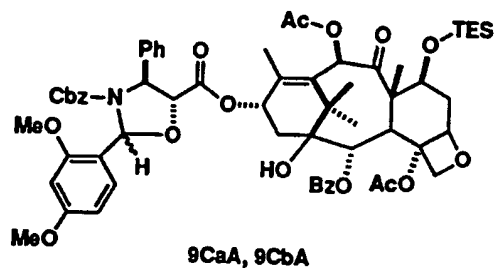


10
BD $R_b = H, R_c = C(O)OCH_2CHCl_2$
BE $R_b = C(O)OCH_2CHCl_2, R_c = H$
BF $R_b = H, R_c = H$ Taxotere

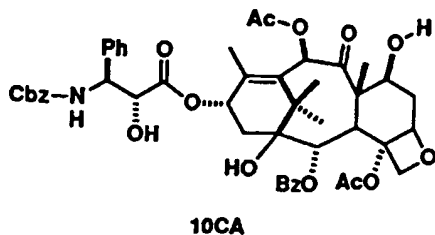
30



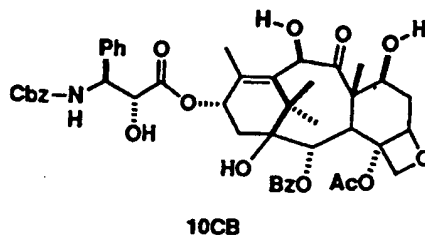
35



40



45



50

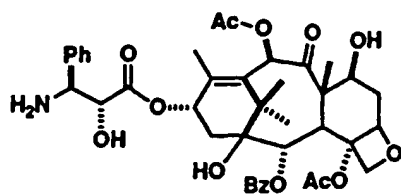
Cbz = $C(O)OCH_2C_6H_5$

FORMULA CHART

cont.

5

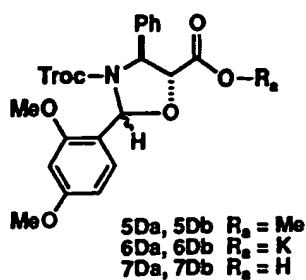
10



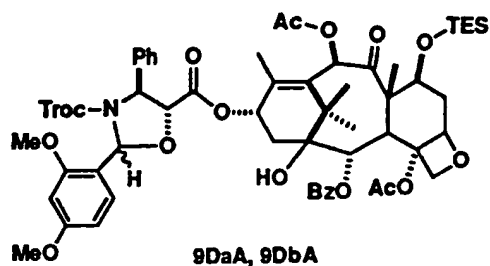
11A

15

20



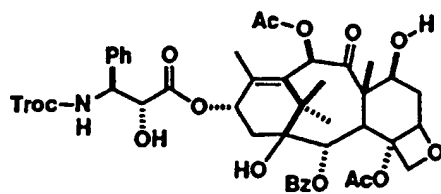
25



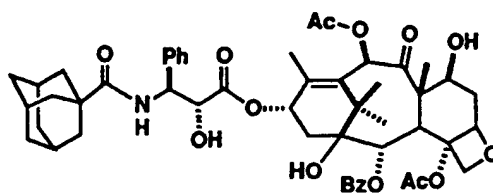
9DaA, 9DbA

30

35



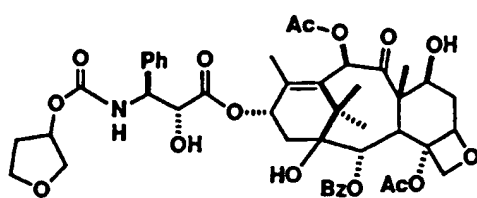
10DA



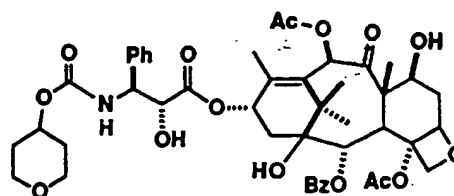
10EA

40

45



10FA

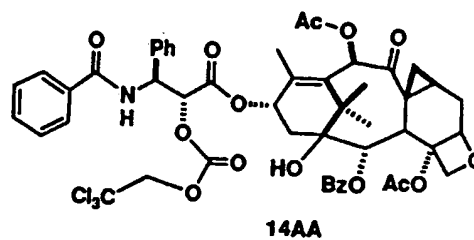
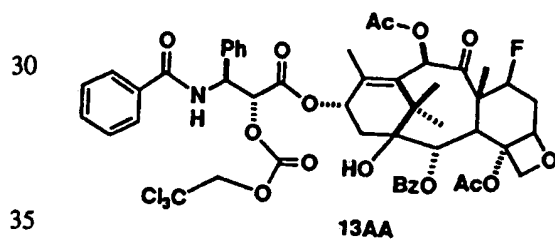
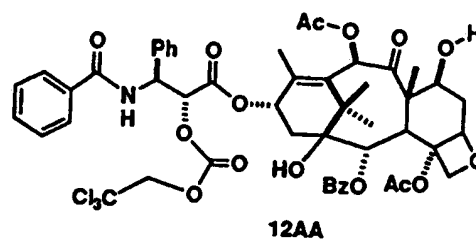
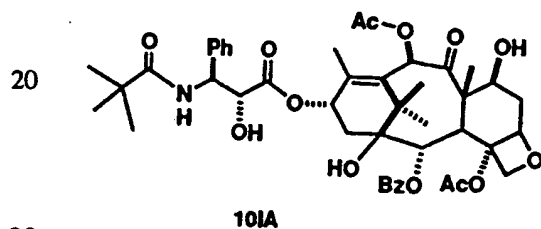
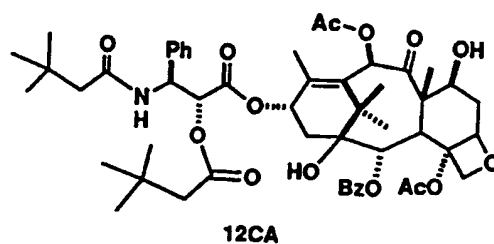
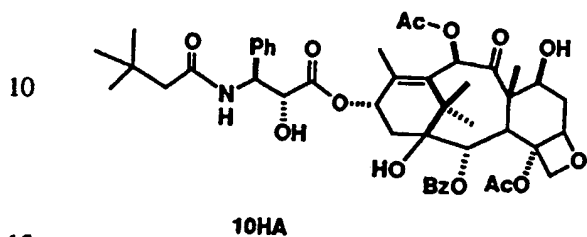


10GA

50

FORMULA CHART
cont.

5



40

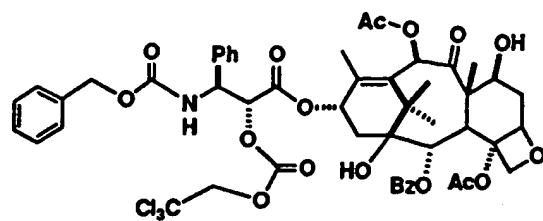
45

50

FORMULA CHART
cont.

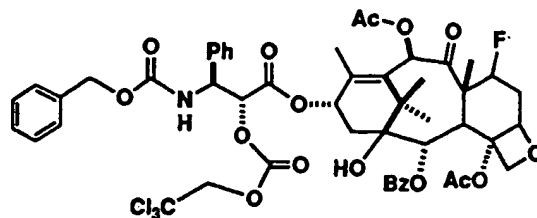
5

10



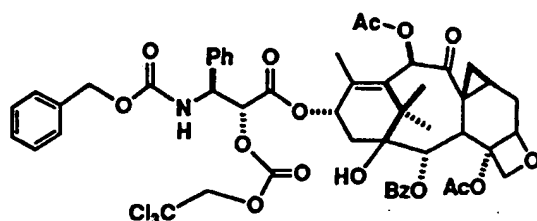
12BA

15



13BA

20



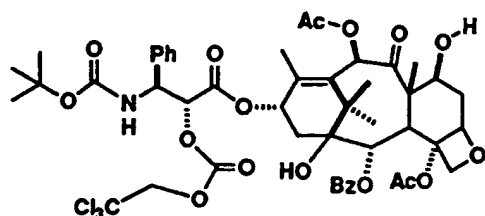
14BA

25

30

35

40



12DA

45

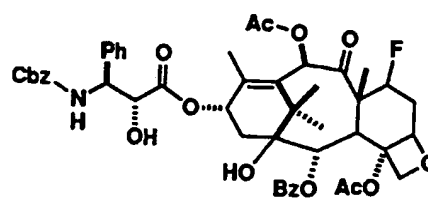
50

FORMULA CHART

cont.

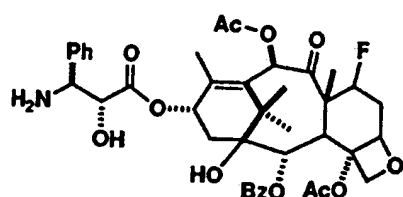
5

10



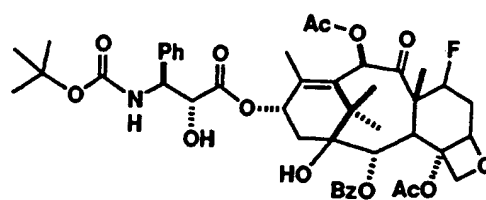
18

15



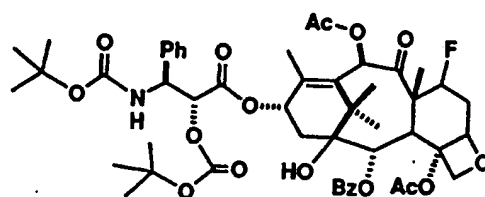
19

20



20

25



13CA

30

35

40

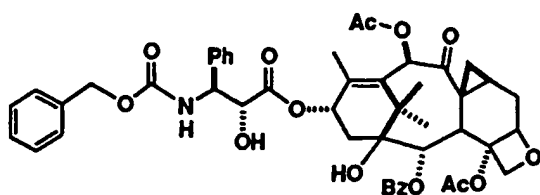
45

50

FORMULA CHART
cont.

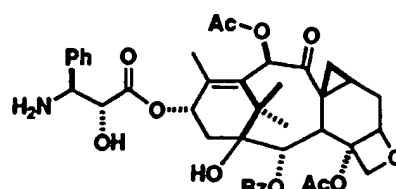
5

10



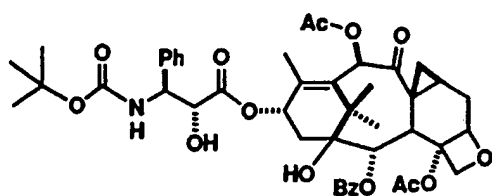
21

15

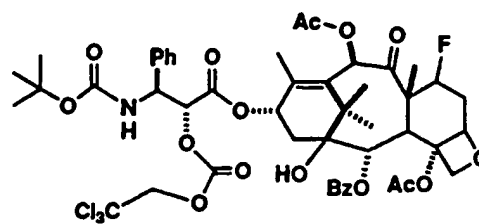


22

20



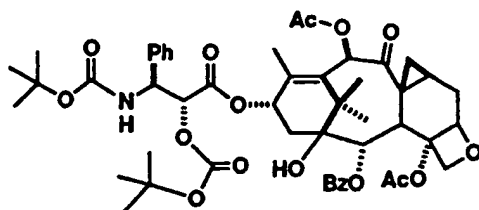
23



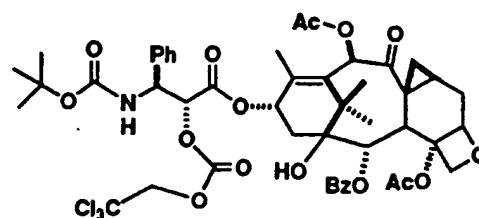
13DA

25

30



14CA



14DA

35

40

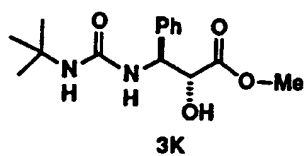
45

50

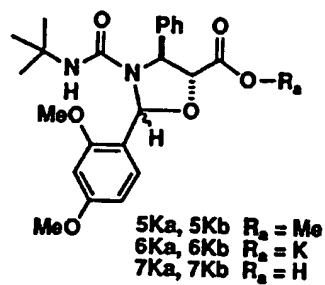
FORMULA CHART
cont.

5

10

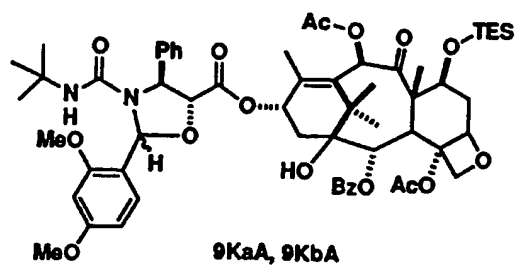


15



20

25



30

35

40

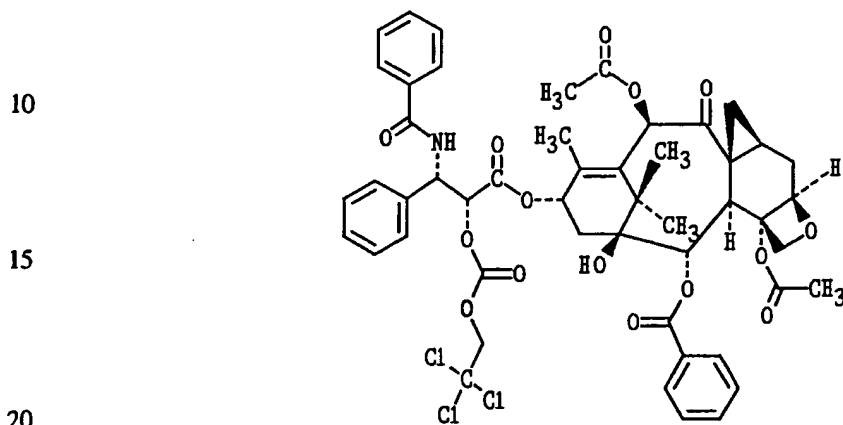
45

50

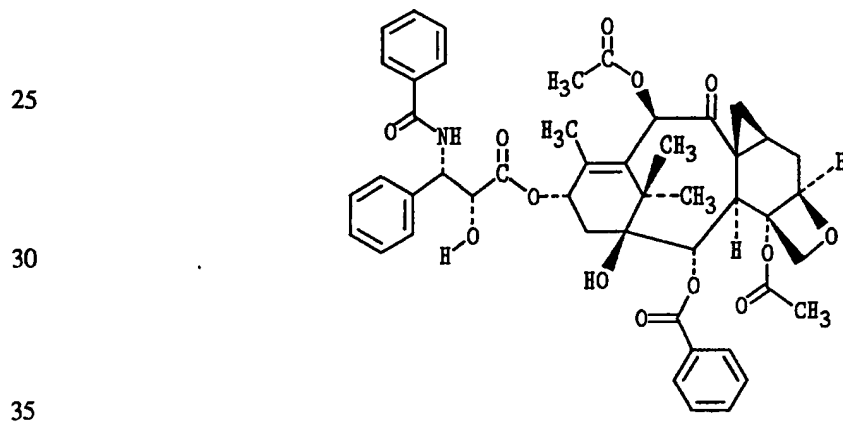
-101-

FORMULA CHART
cont.

5 Compound IIa



Compound IIb



40

45

50

-102-

FORMULA CHART
cont.

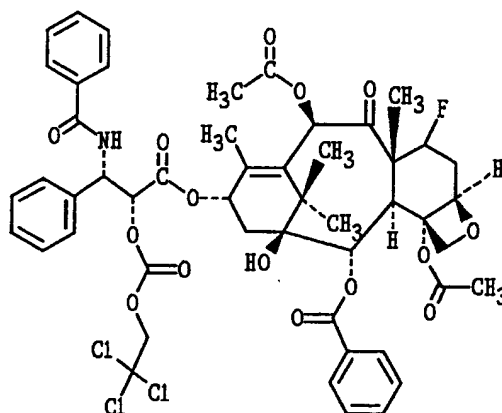
Compound IIIa

5

10

15

20



Compound IIIb

25

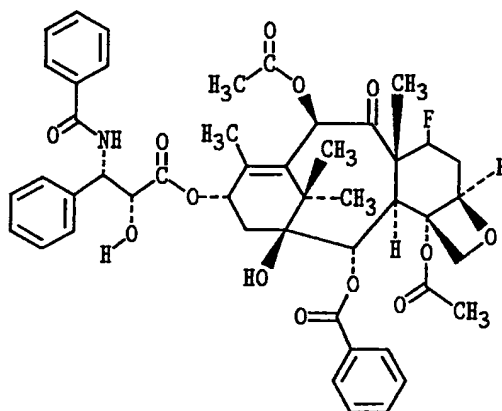
30

35

40

45

50



-103-

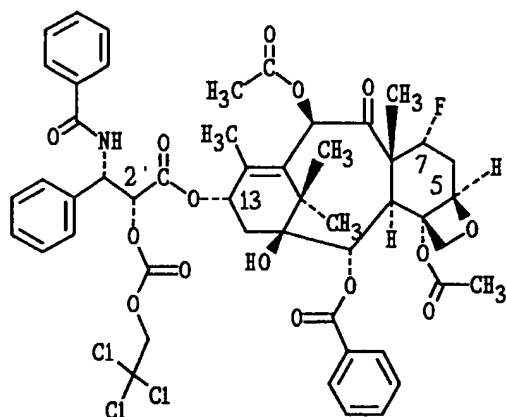
FORMULA CHART
cont.Compound IIIa α

5

10

15

20

Compound IIIa β

25

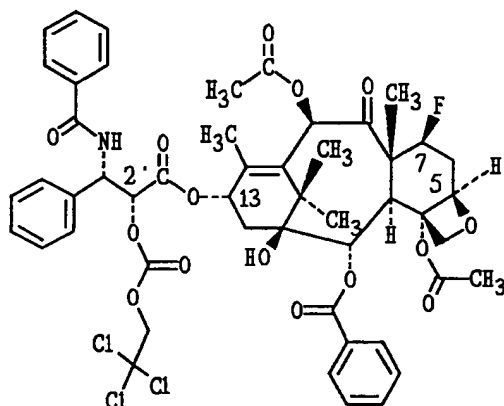
30

35

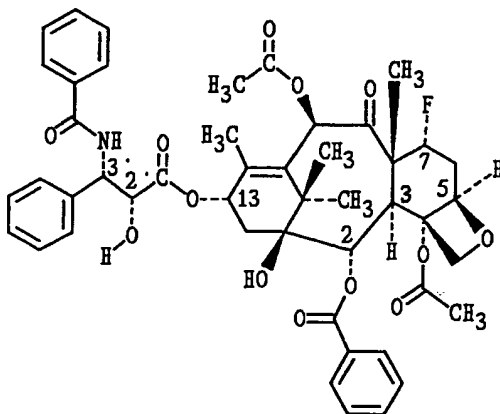
40

45

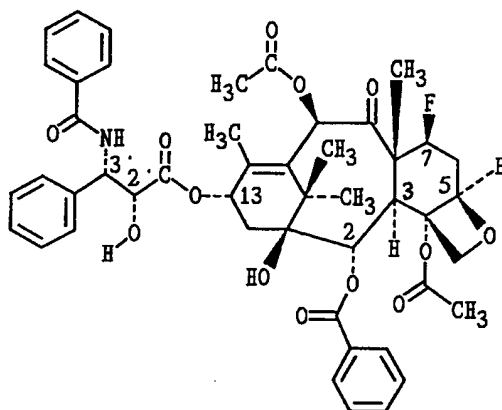
50



5



Compound IIГbβ



45

50

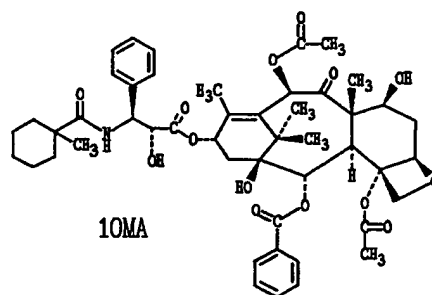
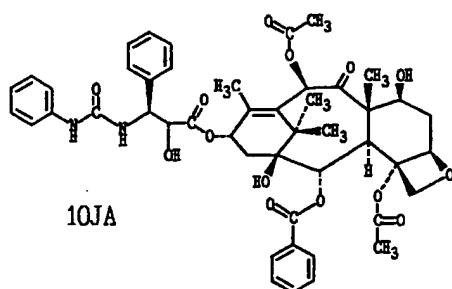
-105-

FORMULA CHART
cont.

5

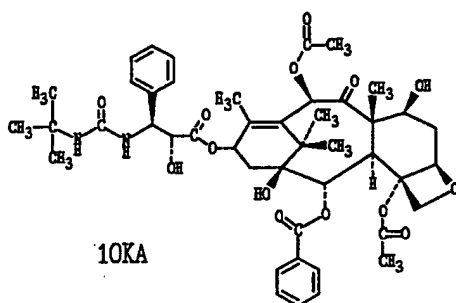
10

15

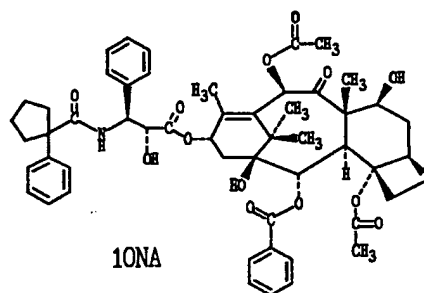


20

25

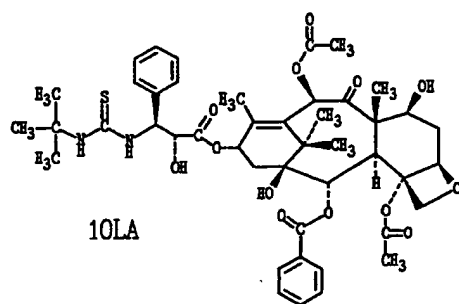


30

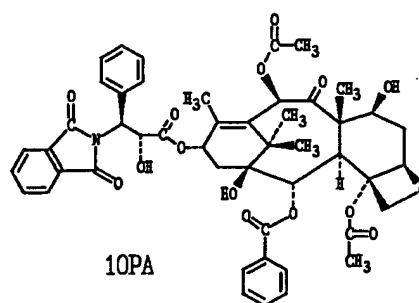


35

40



45



50

-106-

FORMULA CHART
cont.

5

10

15

20

25

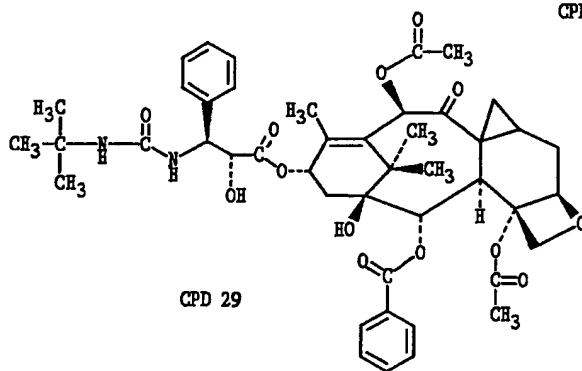
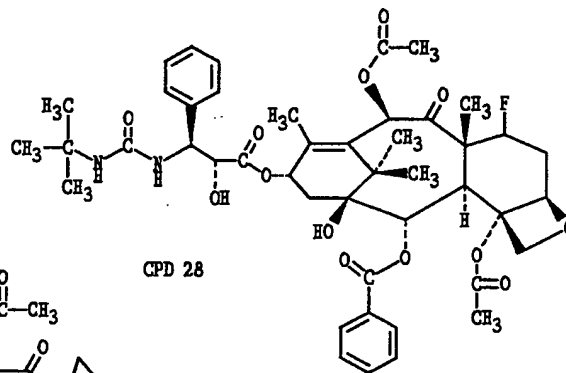
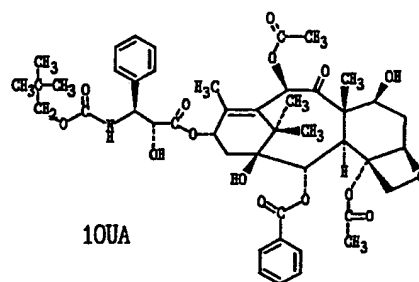
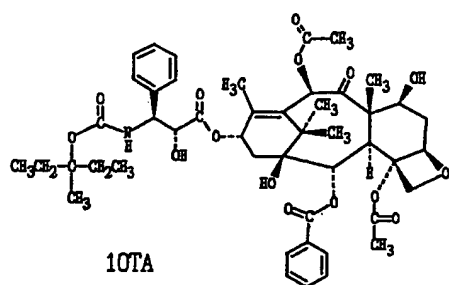
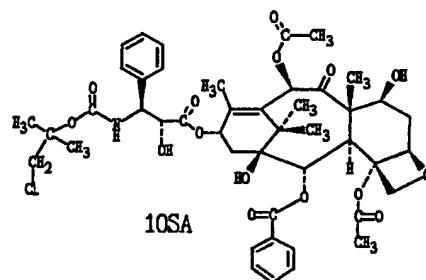
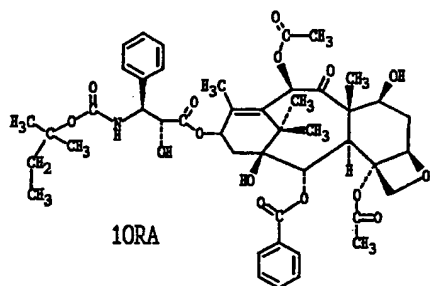
30

35

40

45

50

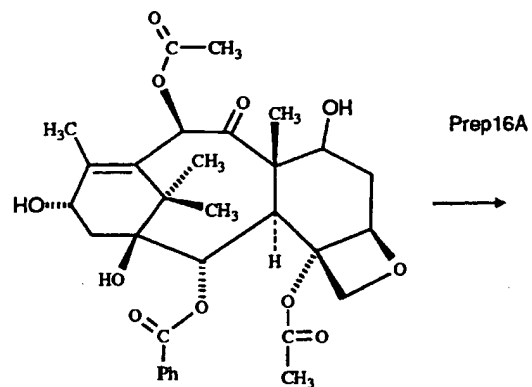


FORMULA CHART
cont.

5

10

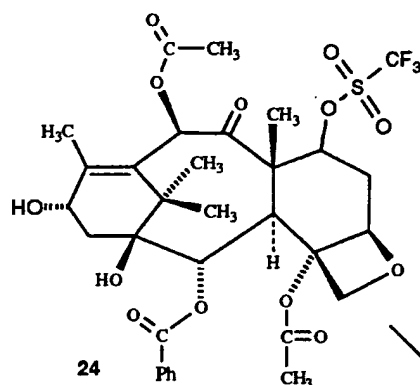
15



20

25

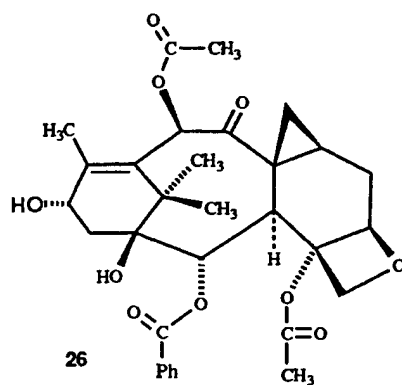
30



35

40

45



50

Prep 16A

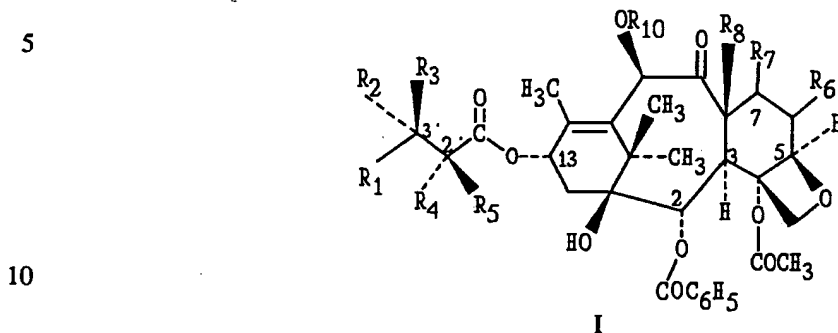
Prep 18A

Prep 19A

-108-

CLAIMS

1. A compound of the Formula I:



wherein:

R_1 is selected from the group consisting of

-CH₃,

- 15 -C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro,

-2-furyl, 2-thienyl, 1-naphthyl, 2-naphthyl or 3,4-methylenedioxyphenyl;

R_2 is selected from the group consisting of -H, -NHC(O)H, -NHC(O)C₁-C₁₀alkyl,

-NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo,

- 20 C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro, -NHC(O)C(CH₃)=CHCH₃,
 -NHC(O)OC(CH₃)₃, -NHC(O)OCH₂phenyl, -NH₂, -NHSO₂-4-methylphenyl, -NHC(O)(CH₂)₃COOH,
 -NHC(O)-4-(SO₃H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranlyl,
 -NHC(O)O-4-tetrahydropyranlyl, -NHC(O)CH₂C(CH₃)₃, -NHC(O)C(CH₃)₃, -NHC(O)OC₁-C₁₀alkyl,
 -NHC(O)NHC₁-C₁₀alkyl, -NHC(O)NHPh, -NHC(O)NHPh substituted with one, 2 or 3 C₁-C₄ alkyl,
 25 C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, or nitro,

-NHC(O)C₃-C₈cycloalkyl, -NHC(O)C(CH₂CH₂)₂CH₃, -NHC(O)C(CH₃)₂CH₂Cl,

-NHC(O)C(CH₃)₂CH₂CH₃, phthalimido, -NHC(O)-1-phenyl-1-cyclopentyl,

-NHC(O)-1-methyl-1-cyclohexyl, -NHC(S)NHC(CH₃)₃, -NHC(O)NHCC(CH₃)₃ or -NHC(O)NHPh;

R_3 is selected from the group consisting of -H, -NHC(O)phenyl or -NHC(O)OC(CH₃)₃, with

- 30 the overall proviso that one of R_2 and R_3 is -H but R_2 and R_3 are not both -H;

R_4 is -H or selected from the group consisting of -OH, -OAc (-OC(O)CH₃),

-OC(O)OCH₂C(Cl)₃, -OCOCH₂CH₂NH₃⁺ HCOO⁻, -NHC(O)phenyl, -NHC(O)OC(CH₃)₃,

-OCOCH₂-CH₂COOH and pharmaceutically acceptable salts thereof, -OCO(CH₂)₃COOH and pharmaceutically acceptable salts thereof, and -OC(O)-Z-C(O)-R' [where Z is ethylene (-CH₂CH₂-),

- 35 propylene (-CH₂CH₂CH₂-), -CH=CH-, 1,2-cyclohexane or 1,2-phenylene, R' is -OH, -OH base,
 -NR'₂R'₃, -OR'₃, -SR'₃, -OCH₂C(O)NR'₄R'₅ where R'₂ is -H or -CH₃, R'₃ is -(CH₂)_nNR'₆R'₇ or

- (CH₂)_nN⁺R'₆R'₇R'₈ X⁻ where n is 1-3, R'₄ is -H or -C₁-C₄alkyl, R'₅ is -H, -C₁-C₄alkyl, benzyl, hydroxyethyl, -CH₂CO₂H or dimethylaminoethyl, R'₆ and R'₇ are -CH₃, -CH₂CH₃, benzyl or R'₆ and R'₇ together with the nitrogen of NR'₆R'₇ form a pyrrolidino, piperidino, morpholino, or N-methylpiperizino group; R'₈ is -CH₃, -CH₂CH₃ or benzyl, X⁻ is halide, and base is NH₃,
 5 (HOC₂H₄)₃N, N(CH₃)₃, CH₃N(C₂H₄)₂NH, NH₂(CH₂)₆NH₂, N-methylglucamine, NaOH or KOH),
 -OC(O)(CH₂)_nNR²R³ [where n is 1-3, R² is -H or -C₁-C₃alkyl and R³ is -H or -C₁-C₃alkyl],
 -OC(O)CH(R'')NH₂ [where R'' is selected from the group consisting of -H, -CH₃, -CH₂CH(CH₃)₂,
 -CH(CH₃)CH₂CH₃, -CH(CH₃)₂, -CH₂phenyl, -(CH₂)₄NH₂, -CH₂CH₂COOH,
 -(CH₂)₃NHC(=NH)NH₂], the residue of the amino acid proline, -OC(O)CH=CH₂,
 10 -C(O)CH₂CH₂C(O)NHCH₂CH₂SO₃⁻ Y⁺, -OC(O)CH₂CH₂C(O)NHCH₂CH₂CH₂SO₃⁻ Y⁺ wherein Y⁺
 is Na⁺ or N⁺(Bu)₄, -OC(O)CH₂CH₂C(O)OCH₂CH₂OH;

R₅ is -H or -OH, with the overall proviso that when R₅ is -OH, R₄ is -H and with the further proviso that when R₅ is -H, R₄ is other than -H;

- R₆ is -H:-H when R₇ is α-R₇₁:β-R₇₂ where one of R₇₁ and R₇₂ is -H and the other of R₇₁
 15 and R₇₂ is -X where X is halo and R₈ is -CH₃;

R₆ is -H:-H when R₇ is α-H:β-R₇₄ where R₇₄ and R₈ are taken together to form a cyclopropyl ring;

- R₁₀ is -H or -C(O)CH₃; and
 pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic
 20 functional group.

2. A compound according to Claim 1 wherein R₂ is -NHC(O)C₆H₅, R₄ is hydroxy, R₃ and R₅ are -H, and R₁ is phenyl or substituted phenyl.
- 25 3. A compound according to Claim 1 wherein R₂ is -NHC(O)OC(CH₃)₃, R₁ is phenyl or substituted phenyl, R₄ is hydroxy, and R₃ and R₅ are -H.
4. A compound according to Claim 1 wherein R₆ is -H:-H when R₇ is α-R₇₁:β-R₇₂ where one of R₇₁ and R₇₂ is -H and the other of R₇₁ and R₇₂ is -X where X is halo and R₈ is -CH₃.
- 30 5. A compound according to Claim 4 selected from the group consisting of 7-deoxy-7α-fluorotaxol, 7-deoxy-7β-fluorotaxol, 2'-[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7α-fluorotaxol and 2'-[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7β-fluorotaxol.
- 35 6. A compound according to Claim 1 wherein R₆ is -H:-H when R₇ is α-H:β-R₇₄ where R₇₄ and R₈ are taken together to form a cyclopropyl group.

7. A compound according to Claim 6 selected from the group consisting of 7-deoxy-7 β ,8 β -methano-taxol and 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7 β ,8 β -methano-taxol.

8. A compound according to Claim 1 selected from the group consisting of
 - 5 7-deoxy-7-fluorotaxol;
 - 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7-fluorotaxol;
 - 2'-succinyl-7-deoxy-7-fluorotaxol;
 - 2'-(β -alanyl)-7-deoxy-7-fluorotaxolformate;
 - 2'-glutaryl-7-deoxy-7-fluorotaxol;
 - 10 2'-[-C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7-fluorotaxol;
 - 2'-(β -sulfofpropionyl)-7-deoxy-7-fluorotaxol;
 - 2'-(2-sulfoethylamido)succinyl-7-deoxy-7-fluorotaxol;
 - 2'-(3-sulfofpropylamido)succinyl-7-deoxy-7-fluorotaxol;
 - 2'-(triethylsilyl)-7-deoxy-7-fluorotaxol;
 - 15 2'-(*t*-butyldimethylsilyl)-7-deoxy-7-fluorotaxol;
 - 2'-(*N,N*-diethylaminopropionyl)-7-deoxy-7-fluorotaxol;
 - 2'-(*N,N*-dimethylglycyl)-7-deoxy-7-fluorotaxol;
 - 2'-(glycyl)-7-deoxy-7-fluorotaxol;
 - 2'-(*L*-alanyl)-7-deoxy-7-fluorotaxol;
 - 20 2'-(*L*-leucyl)-7-deoxy-7-fluorotaxol;
 - 2'-(*L*-isoleucyl)-7-deoxy-7-fluorotaxol;
 - 2'-(*L*-valyl)-7-deoxy-7-fluorotaxol;
 - 2'-(*L*-phenylalanyl)-7-deoxy-7-fluorotaxol;
 - 2'-(*L*-prolyl)-7-deoxy-7-fluorotaxol;
 - 25 2'-(*L*-lysyl)-7-deoxy-7-fluorotaxol;
 - 2'-(*L*-glutamyl)-7-deoxy-7-fluorotaxol;
 - 2'-(*L*-arginyl)-7-deoxy-7-fluorotaxol;
 - N-Debenzoyl-N-tetrahydropyran-4-yloxy carbonyl-7-deoxy-7-fluorotaxol;
 - N-Debenzoyl-N-pivaloyl-7-deoxy-7-fluorotaxol;
 - 30 N-Debenzoyl-N-*n*-hexylaminocarbonyl-7-deoxy-7-fluorotaxol;
 - N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7-fluorotaxol;
 - 7-deoxy-7 α -fluorotaxol;
 - 7-deoxy-7 β -fluorotaxol;
 - 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7 α -fluorotaxol;
 - 35 2'-[[(2,2,2-trichloroethyl)oxy]carbonyl]-7-deoxy-7 β -fluorotaxol;
 - 2'-succinyl-7-deoxy-7 α -fluorotaxol;

- 2'-(β -alanyl)-7-deoxy-7 α -fluorotaxolformate;
2'-glutaryl-7-deoxy-7 α -fluorotaxol;
2'-[-C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7 α -fluorotaxol;
2'-(β -sulfopropionyl)-7-deoxy-7 α -fluorotaxol;
5 2'-(2-sulfoethylamido)succinyl-7-deoxy-7 α -fluorotaxol;
2'-(3-sulfopropylamido)succinyl-7-deoxy-7 α -fluorotaxol;
2'-(triethylsilyl)-7-deoxy-7 α -fluorotaxol;
2'-(*t*-butyldimethylsilyl)-7-deoxy-7 α -fluorotaxol;
2'-(*N,N*-diethylaminopropionyl)-7-deoxy-7 α -fluorotaxol;
10 2'-(*N,N*-dimethylglycyl)-7-deoxy-7 α -fluorotaxol;
2'-(glycyl)-7-deoxy-7 α -fluorotaxol;
2'-(*L*-alanyl)-7-deoxy-7 α -fluorotaxol;
2'-(*L*-leucyl)-7-deoxy-7 α -fluorotaxol;
2'-(*L*-isoleucyl)-7-deoxy-7 α -fluorotaxol;
15 2'-(*L*-valyl)-7-deoxy-7 α -fluorotaxol;
2'-(*L*-phenylalanyl)-7-deoxy-7 α -fluorotaxol;
2'-(*L*-prolyl)-7-deoxy-7 α -fluorotaxol;
2'-(*L*-lysyl)-7-deoxy-7 α -fluorotaxol;
2'-(*L*-glutamyl)-7-deoxy-7 α -fluorotaxol;
20 2'-(*L*-arginyl)-7-deoxy-7 α -fluorotaxol;
2'-succinyl-7-deoxy-7 β -fluorotaxol;
2'-(β -alanyl)-7-deoxy-7 β -fluorotaxolformate;
2'-glutaryl-7-deoxy-7 β -fluorotaxol;
2'-[-C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7 β -fluorotaxol;
25 2'-(β -sulfopropionyl)-7-deoxy-7 β -fluorotaxol;
2'-(2-sulfoethylamido)succinyl-7-deoxy-7 β -fluorotaxol;
2'-(3-sulfopropylamido)succinyl-7-deoxy-7 β -fluorotaxol;
2'-(triethylsilyl)-7-deoxy-7 β -fluorotaxol;
2'-(*t*-butyldimethylsilyl)-7-deoxy-7 β -fluorotaxol;
30 2'-(*N,N*-diethylaminopropionyl)-7-deoxy-7 β -fluorotaxol;
2'-(*N,N*-dimethylglycyl)-7-deoxy-7 β -fluorotaxol;
2'-(glycyl)-7-deoxy-7 β -fluorotaxol;
2'-(*L*-alanyl)-7-deoxy-7 β -fluorotaxol;
2'-(*L*-leucyl)-7-deoxy-7 β -fluorotaxol;
35 2'-(*L*-isoleucyl)-7-deoxy-7 β -fluorotaxol;
2'-(*L*-valyl)-7-deoxy-7 β -fluorotaxol;

-112-

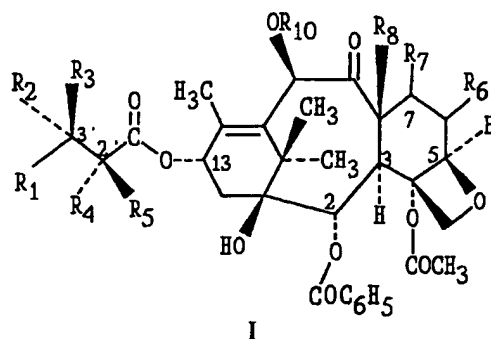
- 2'-(L-phenylalanyl)-7-deoxy-7 β -fluorotaxol;
 2'-(L-prolyl)-7-deoxy-7 β -fluorotaxol;
 2'-(L-lysyl)-7-deoxy-7 β -fluorotaxol;
 2'-(L-glutamyl)-7-deoxy-7 β -fluorotaxol;
 5 2'-(L-arginyl)-7-deoxy-7 β -fluorotaxol;
 7-deoxy-7 β ,8 β -methano-taxol;
 2'-[[(2,2,2-trichloroethyl)oxy] carbonyl]-7-deoxy-7 β ,8 β -methano-taxol;
 2'-succinyl-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(β -alanyl)-7-deoxy-7 β ,8 β -methano-taxolformate;
 10 2'-glutaryl-7-deoxy-7 β ,8 β -methano-taxol;
 2'-[C(O)(CH₂)₃C(O)NH(CH₂)₃N(CH₃)₂]-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(β -sulfopropionyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(2-sulfoethylamido)succinyl-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(3-sulfopropylamido)succinyl-7-deoxy-7 β ,8 β -methano-taxol;
 15 2'-(triethylsilyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(*t*-butyldimethylsilyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(N,N-diethylaminopropionyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(N,N-dimethylglycyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(glycyl)-7-deoxy-7 β ,8 β -methano-taxol;
 20 2'-(L-alanyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(L-leucyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(L-isoleucyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(L-valyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(L-phenylalanyl)-7-deoxy-7 β ,8 β -methano-taxol;
 25 2'-(L-prolyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(L-lysyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(L-glutamyl)-7-deoxy-7 β ,8 β -methano-taxol;
 2'-(L-arginyl)-7-deoxy-7 β ,8 β -methano-taxol;
 7-deoxy-7 β ,8 β -methano-taxotere;
 30 N-Debenzoyl-N-tetrahydrofuran-3-yloxycarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(1-adamantoyl)-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-phenylaminocarbonyl-7-deoxy-7 β ,8 β -methanotaxol; or
 N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7 β ,8 β -methano-taxol.

35

9. A pharmaceutical composition comprising an effective antitumor amount of at least one compound of the Formula I:

5

10



wherein:

15

R_1 is selected from the group consisting of

-CH₃,

-C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro, 2-furyl, 2-thienyl, 1-naphthyl, 2-naphthyl or 3,4-methylenedioxyphenyl;

R_2 is selected from the group consisting of -H, -NHC(O)H, -NHC(O)C₁-C₁₀alkyl,

20

-NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro, -NHC(O)C(CH₃)=CHCH₃, -NHC(O)OC(CH₃)₃, -NHC(O)OCH₂phenyl, -NH₂, -NHSO₂-4-methylphenyl, -NHC(O)(CH₂)₃COOH, -NHC(O)-4-(SO₃H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranlyl, -NHC(O)O-4-tetrahydropyranlyl, -NHC(O)CH₂C(CH₃)₃, -NHC(O)C(CH₃)₃, -NHC(O)OC₁-C₁₀alkyl, -NHC(O)NHC₁-C₁₀alkyl, NHC(O)NHPh, -NHC(O)NHPh substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, or nitro, -NHC(O)C₃-C₈cycloalkyl, -NHC(O)C(CH₂CH₃)₂CH₃, -NHC(O)C(CH₃)₂CH₂Cl, -NHC(O)C(CH₃)₂CH₂CH₃, phthalimido, -NHC(O)-1-phenyl-1-cyclopentyl, -NHC(O)-1-methyl-1-cyclohexyl, -NHC(S)NHC(CH₃)₃, -NHC(O)NHCC(CH₃)₃ or -NHC(O)NHPh;

30

R_3 is selected from the group consisting of -H, -NHC(O)phenyl or -NHC(O)OC(CH₃)₃, with the overall proviso that one of R_2 and R_3 is -H but R_2 and R_3 are not both -H;

R_4 is -H or selected from the group consisting of -OH, -OAc (-OC(O)CH₃),

-OC(O)OCH₂C(Cl)₃, -OCOCH₂CH₂NH₃⁺ HCOO⁻, -NHC(O)phenyl, -NHC(O)OC(CH₃)₃, -OCOCH₂CH₂COOH and pharmaceutically acceptable salts thereof, -OCO(CH₂)₃COOH and pharmaceutically acceptable salts thereof, and -OC(O)-Z-C(O)-R' [where Z is ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), -CH=CH-, 1,2-cyclohexane or 1,2-phenylene, R' is -OH, -OH base,

35

-114-

- NR'₂R'₃, -OR'₃, -SR'₃, -OCH₂C(O)NR'₄R'₅ where R'₂ is -H or -CH₃, R'₃ is -(CH₂)_nNR'₆R'₇ or (CH₂)_nN⁺R'₆R'₇R'₈ X⁻ where n is 1-3, R'₄ is -H or -C₁-C₄alkyl, R'₅ is -H, -C₁-C₄alkyl, benzyl, hydroxyethyl, -CH₂CO₂H or dimethylaminoethyl, R'₆ and R'₇ are -CH₃, -CH₂CH₃, benzyl or R'₆ and R'₇ together with the nitrogen of NR'₆R'₇ form a pyrrolidino, piperidino, morpholino, or
- 5 N-methylpiperizino group; R'₈ is -CH₃, -CH₂CH₃ or benzyl, X⁻ is halide, and base is NH₃, (HOC₂H₄)₃N, N(CH₃)₃, CH₃N(C₂H₄)₂NH, NH₂(CH₂)₆NH₂, N-methylglucamine, NaOH or KOH], -OC(O)(CH₂)_nNR²R³ [where n is 1-3, R² is -H or -C₁-C₃alkyl and R³ is -H or -C₁-C₃alkyl], -OC(O)CH(R'')NH₂ [where R'' is selected from the group consisting of -H, -CH₃, -CH₂CH(CH₃)₂, -CH(CH₃)CH₂CH₃, -CH(CH₃)₂, -CH₂phenyl, -(CH₂)₄NH₂, -CH₂CH₂COOH,
- 10 -(CH₂)₃NHC(=NH)NH₂], the residue of the amino acid proline, -OC(O)CH=CH₂, -C(O)CH₂CH₂C(O)NHCH₂CH₂SO₃⁻Y⁺, -OC(O)CH₂CH₂C(O)NHCH₂CH₂CH₂SO₃⁻Y⁺ wherein Y⁺ is Na⁺ or N⁺(Bu)₄, -OC(O)CH₂CH₂C(O)OCH₂CH₂OH;

R₅ is -H or -OH, with the overall proviso that when R₅ is -OH, R₄ is -H and with the further proviso that when R₅ is -H, R₄ is other than -H;

- 15 R₆ is -H:-H when R₇ is α-R₇₁:β-R₇₂ where one of R₇₁ and R₇₂ is -H and the other of R₇₁ and R₇₂ is -X where X is halo and R₈ is -CH₃;

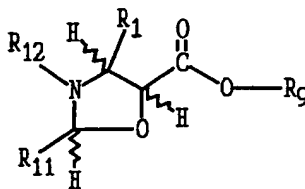
R₆ is -H:-H when R₇ is α-H:β-R₇₄ where R₇₄ and R₈ are taken together to form a cyclopropyl ring;

R₁₀ is -H or -C(O)CH₃; and

- 20 pharmaceutically acceptable salts thereof when the compound contains either an acidic or basic functional group.

10. A process for preparing oxazolidines of Formula 5

25

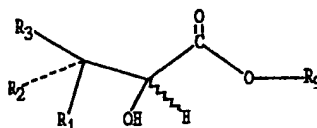


- 30 R₁ is selected from the group consisting of -CH₃, -C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro, -2-furyl, 2-thienyl, 1-naphthyl, 2-naphthyl or 3,4-methylenedioxyphenyl;
- 35 R₉ is selected from C₁-C₆alkyl;
- R₁₁ is phenyl substituted with -(OC₁-C₂alkyl)_n where n is 1 to 3;

-115-

- R_{12} is selected from the group consisting of $-C(O)H$, $-C(O)C_1-C_{10}alkyl$, $-C(O)phenyl$, $-C(O)phenyl$ substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, $-C(O)C(CH_3)=CHCH_3$, $-C(O)OC(CH_3)_3$, $-C(O)OCH_2phenyl$, $-SO_2-4-methylphenyl$, $-C(O)(CH_2)_3COOH$, $-C(O)-4-(SO_3H)phenyl$,
- 5 $-C(O)-1-adamantyl$, $-C(O)O-3-tetrahydrofuranyl$, $-C(O)O-4-tetrahydropyranyl$, $-C(O)CH_2C(CH_3)_3$, $-C(O)C(CH_3)_3$, $-C(O)OC_1-C_{10}alkyl$, $-C(O)NHC_1-C_{10}alkyl$, $-NHC(O)NHPh$, $-NHC(O)NHPh$ substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, $-NHC(O)C_3-C_8cycloalkyl$, $-NHC(O)C(CH_2CH_3)_2CH_3$, $-NHC(O)C(CH_3)_2CH_2Cl$, $-NHC(O)C(CH_3)_2CH_2CH_3$, phthalimido, $-NHC(O)-1-phenyl-1-cyclopentyl$,
- 10 $-NHC(O)-1-methyl-1-cyclohexyl$, $-NHC(S)NHC(CH_3)_3$, $-NHC(O)NHCC(CH_3)_3$ or $-NHC(O)NHPh$;
which comprises reacting a hydroxy-amine of Formula 3

15

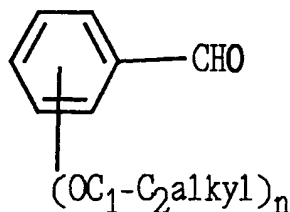


in which

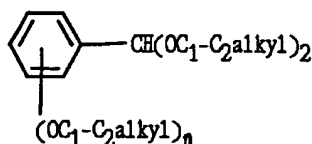
- 20 R_1 and R_9 are as defined above;
- R_2 is selected from the group consisting of $-NHC(O)H$, $-NHC(O)C_1-C_{10}alkyl$, $-NHC(O)phenyl$, $-NHC(O)phenyl$ substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, hydroxy or nitro, $-NHC(O)C(CH_3)=CHCH_3$, $-NHC(O)OC(CH_3)_3$, $-NHC(O)OCH_2phenyl$, $-NHSO_2-4-methylphenyl$, $-NHC(O)(CH_2)_3COOH$,
- 25 $-NHC(O)-4-(SO_3H)phenyl$, $-NHC(O)-1-adamantyl$, $-NHC(O)O-3-tetrahydrofuranyl$, $-NHC(O)O-4-tetrahydropyranyl$, $-NHC(O)CH_2C(CH_3)_3$, $-NHC(O)C(CH_3)_3$, $-NHC(O)OC_1-C_{10}alkyl$, $-NHC(O)NHC_1-C_{10}alkyl$, $-NHC(O)NHPh$ optionally substituted with one, 2 or 3 C_1-C_4 alkyl, C_1-C_3 alkoxy, halo, C_1-C_3 alkylthio, trifluoromethyl, C_2-C_6 dialkylamino, or nitro, $-NHC(O)C_3-C_8cycloalkyl$, $-NHC(O)C(CH_2CH_3)CH_3$, $-NHC(O)C(CH_3)_2CH_2Cl$,
- 30 $-NHC(O)C(CH_3)_2CH_2CH_3$, phthalimido, $-NHC(O)-1-phenyl-1-cyclopentyl$, $-NHC(O)-1-methyl-1-cyclohexyl$, $-NHC(S)NHC(CH_3)_3$, $-NHC(O)NHCC(CH_3)_3$ or $-NHC(O)NHPh$;
- R_3 is selected from the group consisting of $-H$, $-NHC(O)phenyl$ or $-NHC(O)OC(CH_3)_3$, with the overall proviso that one of R_2 and R_3 is $-H$ but R_2 and R_3 are not both $-H$;

-116-

with (1) a benzaldehyde of Formula 4



or (2) an acetal of Formula 4A

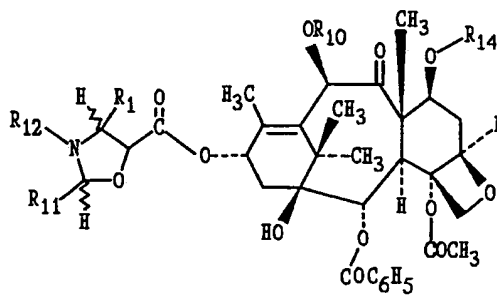


where n is 1-3.

11. A process according to Claim 9 wherein the benzaldehyde is selected from the group consisting of 2-methoxybenzaldehyde, 3-methoxybenzaldehyde, 4-methoxybenzaldehyde, 2,4-dimethoxybenzaldehyde, 3,5-dimethoxybenzaldehyde, 2,5-dimethoxybenzaldehyde, 2,4,6-trimethoxybenzaldehyde, 4-ethoxybenzaldehyde, or 4-methoxybenzaldehyde.

12. A process according to Claim 9 wherein the hydroxy-amine of Formula 3 is reacted with 2,4-dimethoxy benzaldehyde dimethyl acetal.

13. A process of preparing



wherein R₁ is selected from the group consisting of

-117-

-CH₃,

-C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro,

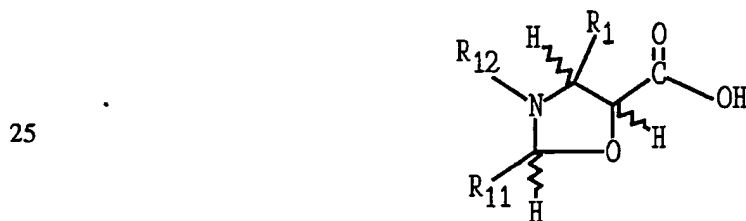
-2-furyl, 2-thienyl, 1-naphthyl, 2-naphthyl or 3,4-methylenedioxyphenyl;

5 R₁₀ is -H or -C(O)CH₃;

R₁₁ is phenyl substituted with -(OC₁-C₂alkyl)_n where n is 1 to 3;

R₁₂ is selected from the group consisting of -C(O)H, -C(O)C₁-C₁₀alkyl, -C(O)phenyl, -C(O)phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro, -C(O)C(CH₃)=CHCH₃, -C(O)OC(CH₃)₃,
 10 -C(O)OCH₂phenyl, -SO₂-4-methylphenyl, -C(O)(CH₂)₃COOH, -C(O)-4-(SO₃H)phenyl, -C(O)-1-adamantyl, -C(O)O-3-tetrahydrofuranyl, -C(O)O-4-tetrahydropyranyl, -C(O)CH₂C(CH₃)₃, -C(O)C(CH₃)₃, -C(O)OC₁-C₁₀alkyl, -C(O)NHC₁-C₁₀alkyl, -NHC(O)NHPh, -NHC(O)NHPh substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, or nitro, -NHC(O)C₃-C₈cycloalkyl, -NHC(O)C(CH₂CH₃)₂CH₃,
 15 -NHC(O)C(CH₃)₂CH₂Cl, -NHC(O)C(CH₃)₂CH₂CH₃, phthalimido, -NHC(O)-1-phenyl-1-cyclopentyl, -NHC(O)-1-methyl-1-cyclohexyl, -NHC(S)NHC(CH₃)₃, -NHC(O)NHCC(CH₃)₃ or -NHC(O)NHPh;
 and

R₁₄ is selected from the group consisting of -C(O)C₁-C₆alkyl, -C(O)OC₁-C₆alkyl, -C(O)OCH₂CX₃ where X is Halo, -C(O)OCH₂CH₂SiR₂₀ (where R₂₀ is C₁-C₆alkyl), or -Si(R₂₀)₃;
 20 which comprises reacting an oxazolidine free acid of Formula 7

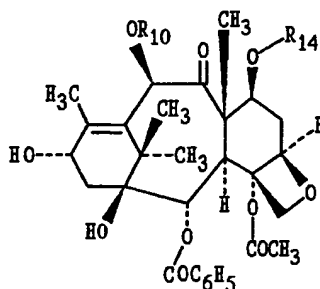


wherein R₁, R₁₁ and R₁₂ are as defined above;

30

-118-

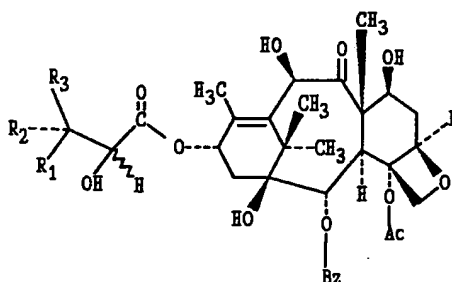
with a baccatin compound of Formula 8



wherein R_{10} and R_{14} are as defined above;

in the presence of a dehydrating agent.

14. A process of preparing a compound of formula:



wherein

R_1 is selected from the group consisting of

-CH₃,

-C₆H₅ or phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo,

C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro,

-2-furyl, 2-thienyl, 1-naphthyl, 2-naphthyl or 3,4-methylenedioxyphenyl;

R_2 is selected from the group consisting of -H, -NHC(O)H, -NHC(O)C₁-C₁₀alkyl,

-NHC(O)phenyl, -NHC(O)phenyl substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo,

C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, hydroxy or nitro, -NHC(O)C(CH₃)=CHCH₃,

-NHC(O)OC(CH₃)₃, -NHC(O)OCH₂phenyl, -NH₂, -NHSO₂-4-methylphenyl, -NHC(O)(CH₂)₃COOH,

-NHC(O)-4-(SO₃H)phenyl, -OH, -NHC(O)-1-adamantyl, -NHC(O)O-3-tetrahydrofuranyl,

-NHC(O)O-4-tetrahydropyranyl, -NHC(O)CH₂C(CH₃)₃, -NHC(O)C(CH₃)₃, -NHC(O)OC₁-C₁₀alkyl,

-NHC(O)NHC₁-C₁₀alkyl, -NHC(O)NHPh, -NHC(O)NHPh substituted with one, 2 or 3 C₁-C₄ alkyl,

C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, or nitro,

-NHC(O)C₃-C₈cycloalkyl, -NHC(O)C(CH₂CH₂)₂CH₃, -NHC(O)C(CH₃)₂CH₂Cl,

-NHC(O)C(CH₃)₂CH₂CH₃, phthalimido, -NHC(O)-1-phenyl-1-cyclopentyl,

-119-

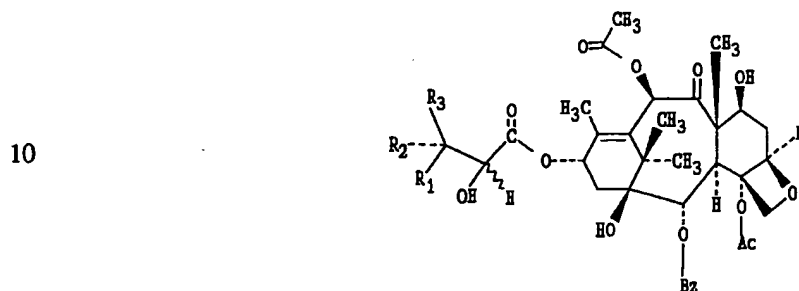
-NHC(O)-1-methyl-1-cyclohexyl, -NHC(S) NHC(CH₃)₃, -NHC(O)NHCC(CH₃)₃ or -NHC(O)NHPh;

R₃ is selected from the group consisting of -H, -NHC(O)phenyl or -NHC(O)OC(CH₃)₃, with the overall proviso that one of R₂ and R₃ is -H but R₂ and R₃ are not both -H;

Bz is -C(O)phenyl; and

5 Ac is C(O)CH₃;

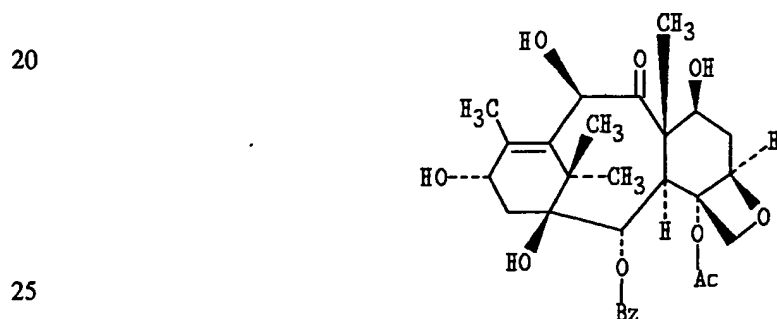
which comprises reacting a compound of formula:



wherein R₁, R₂, R₃, Bz and Ac are as defined above;

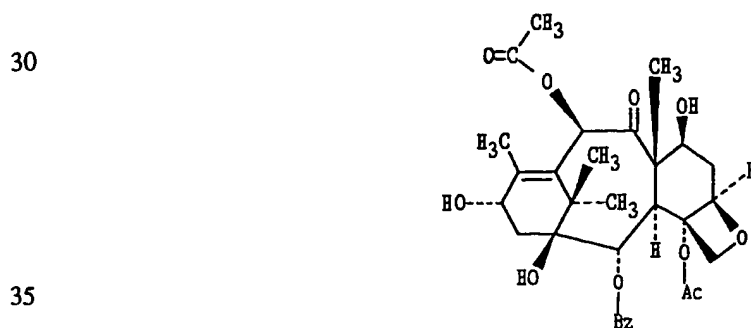
15 with hydrazine.

15. A process of preparing a compound of formula:



wherein Bz is C(O)phenyl and Ac is C(O)CH₃;

which comprises reacting a compound of formula:



with hydrazine.

16. A compound according to Claim 1 selected from the group consisting of 10-acetyl-7-deoxy-7-fluorotaxotere or 10-acetyl-7 β ,8 β -methano-taxotere.
17. A compound according to Claim 1 selected from the group consisting of
 N-Debenzoyl-N-tetrahydrofuran-3-yloxyacarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(1-adamantoyl)-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-phenylaminocarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-t-butylaminocarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(1-methyl-1-cyclohexylanoil)-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(1-phenyl-1-cyclopentanoil)-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-phthalimido-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-t-butylaminothiocarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-t-amyloxyacarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-neopentyloxyacarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(2-chloro-1,1-dimethylethyl)oxyacarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-(3-methyl-3-pentyl)oxyacarbonyl-7-deoxy-7 β ,8 β -methanotaxol;
 N-Debenzoyl-N-tetrahydropyran-4-yloxyacarbonyl-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-pivaloyl-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-n-hexylaminocarbonyl-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-t-butylaminocarbonyl-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-(1-methyl-1-cyclohexylanoil)-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-(1-phenyl-1-cyclopentanoil)-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-phthalimido-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-t-butylaminothiocarbonyl-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-t-amyloxyacarbonyl-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-neopentyloxyacarbonyl-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-(2-chloro-1,1-dimethylethyl)oxyacarbonyl-7-deoxy-7-fluorotaxol;
 N-Debenzoyl-N-(3-methyl-3-pentyl)oxyacarbonyl-7-deoxy-7-fluorotaxol; or
 N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7-fluoro-taxol.
18. A compound according to Claim 1 selected from the group consisting of
 3'-desphenyl-3'-(2-furyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(2-thienyl)-7-deoxy-7 β ,8 β -methanotaxol;
 3'-desphenyl-3'-(1-naphthyl)-7-deoxy-7 β ,8 β -methanotaxol;

- 3'-desphenyl-3'-(2-naphthyl)-7-deoxy-7 β ,8 β -methanotaxol;
3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;
3'-desphenyl-3'-(4-bromophenyl)-7-deoxy-7 β ,8 β -methanotaxol;
5 3'-desphenyl-3'-(3,4-methylenedioxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
3'-desphenyl-3'-(3,4-dimethoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
3'-desphenyl-3'-(4-nitrophenyl)-7-deoxy-7 β ,8 β -methanotaxol;
3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -methanotaxol;
N-debenzoyl-N-(4-bromobenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
10 N-debenzoyl-N-(4-methylbenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
N-debenzoyl-N-(4-t-butylbenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
N-debenzoyl-N-(4-methoxybenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -
methanotaxol;
15 N-debenzoyl-N-(4-fluorobenzoyl)-7-deoxy-7 β ,8 β -methanotaxol;
N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -
methanotaxol;
N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -
methanotaxol;
20 N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -
methanotaxol;
N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -
methanotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -
25 methanotaxol;
N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -
methanotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -
methanotaxol;
30 N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -
methanotaxol;
N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -
methanotaxol;
N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7 β ,8 β -
35 methanotaxol;
N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7 β ,8 β -

- methanotaxol;
N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
5 N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
N-debenzoyl-N-(4-methoxybenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7 β ,8 β -methanotaxol;
10 3'-desphenyl-3'-(2-furyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(2-thienyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(1-naphthyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(2-naphthyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;
15 3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(4-bromophenyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(3,4-methylenedioxyphenyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(3,4-dimethoxyphenyl)-7-deoxy-7-fluorotaxol;
3'-desphenyl-3'-(4-nitrophenyl)-7-deoxy-7-fluorotaxol;
20 3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-bromobenzoyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-methylbenzoyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-t-butylbenzoyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-methoxybenzoyl)-7-deoxy-7-fluorotaxol;
25 N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-fluorotaxol;
30 N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-methylbenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;
fluorotaxol;
N-debenzoyl-N-(4-fluorobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-fluorotaxol;
35 N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-fluorotaxol;
N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-fluorotaxol;

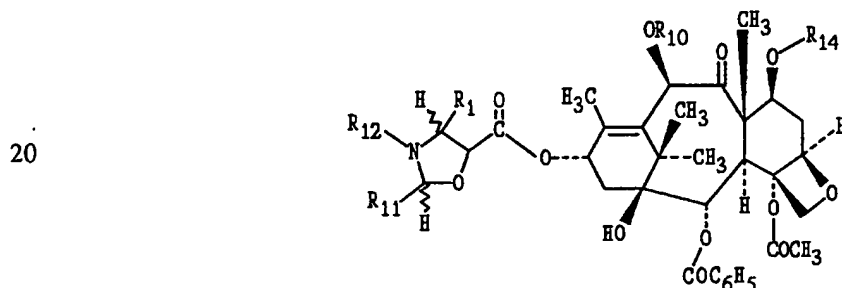
-123-

- N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-chlorophenyl)-7-deoxy-7-fluorotaxol;
 N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-fluorophenyl)-7-deoxy-7-fluorotaxol;
 N-debenzoyl-N-(4-chlorobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;
 N-debenzoyl-N-(4-bromobenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;
 5 N-debenzoyl-N-(4-t-butylbenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol;
 N-debenzoyl-N-(4-methoxybenzoyl)-3'-desphenyl-3'-(4-methoxyphenyl)-7-deoxy-7-fluorotaxol.

19. A compound according to Claim 1 wherein R_2 is $\text{-NHC(O)NHC(CH}_3)_3$, R_4 is hydroxy, R_3 and R_5 are -H , and R_1 is phenyl or substituted phenyl.

20. A compound according to Claim 1 selected from the group consisting of N-debenzoyl-N-(*t*-butyl)aminocarbonyl-7-deoxy-7 β ,8 β -methano-taxol or N-debenzoyl-N-(*t*-butyl)amino-carbonyl-7-deoxy-7-fluoro-taxol.

21. A compound of formula



25 wherein R_1 is selected from the group consisting of

-CH_3 ,

$\text{-C}_6\text{H}_5$ or phenyl substituted with one, 2 or 3 $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_3$ alkoxy, halo, $\text{C}_1\text{-C}_3$ alkylthio, trifluoromethyl, $\text{C}_2\text{-C}_6$ dialkylamino, hydroxy or nitro,

-2-furyl , -2-thienyl , -1-naphthyl , -2-naphthyl or $\text{-3,4-methylenedioxyphenyl}$;

30 R_{11} is phenyl substituted with $\text{-(OC}_1\text{-C}_2\text{alkyl)}_n$ where n is 1 to 3;

R_{12} is selected from the group consisting of -C(O)H , $\text{-C(O)C}_1\text{-C}_{10}\text{alkyl}$, -C(O)phenyl ,

-C(O)phenyl substituted with one, 2 or 3 $\text{C}_1\text{-C}_4$ alkyl, $\text{C}_1\text{-C}_3$ alkoxy, halo, $\text{C}_1\text{-C}_3$ alkylthio, trifluoromethyl, $\text{C}_2\text{-C}_6$ dialkylamino, hydroxy or nitro, $\text{-C(O)C(CH}_3)_2\text{=CHCH}_3$, $\text{-C(O)OC(CH}_3)_3$,

$\text{-C(O)OCH}_2\text{phenyl}$, $\text{-SO}_2\text{-4-methylphenyl}$, $\text{-C(O)(CH}_2)_3\text{COOH}$, $\text{-C(O)-4-(SO}_3\text{H)phenyl}$,

35 -C(O)-1-adamantyl , $\text{-C(O)O-3-tetrahydrofuranyl}$, $\text{-C(O)O-4-tetrahydropyranyl}$, $\text{-C(O)CH}_2\text{C(CH}_3)_3$,

$\text{-C(O)C(CH}_3)_3$, $\text{-C(O)OC}_1\text{-C}_{10}\text{alkyl}$, $\text{-C(O)NHC}_1\text{-C}_{10}\text{alkyl}$, -NHC(O)NHPh , -NHC(O)NHPh

-124-

substituted with one, 2 or 3 C₁-C₄ alkyl, C₁-C₃ alkoxy, halo, C₁-C₃ alkylthio, trifluoromethyl, C₂-C₆ dialkylamino, or nitro, -NHC(O)C₃-C₈cycloalkyl, -NHC(O)C(CH₂CH₃)₂CH₃, -NHC(O)C(CH₃)₂CH₂Cl, -NHC(O)C(CH₃)₂CH₂CH₃, phthalimido, -NHC(O)-1-phenyl-1-cyclopentyl, -NHC(O)-1-methyl-1-cyclohexyl, -NHC(S)NHC(CH₃)₃, -NHC(O)NHCC(CH₃)₃ or -NHC(O)NHPh;

5 and

R₁₀ and R₁₄, being the same or different, are selected from the group consisting of -C(O)C₁-C₆alkyl, -C(O)OC₁-C₆alkyl, -C(O)OCH₂CX₃ where X is Halo, -C(O)OCH₂CH₂SiR₂₀ (where R₂₀ is C₁-C₆alkyl), or -Si(R₂₀)₃.

10

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 93/11827

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D305/14 C07D413/12 C07D263/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 09589 (RHONE-POULENC) 11 June 1992 cited in the application see page 1 - page 15; claims -----	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

22 March 1994

Date of mailing of the international search report

30.03.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 93/11827

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9209589	11-06-92	FR-A- 2669631	29-05-92
		FR-A- 2679557	29-01-93
		AU-A- 9083891	25-06-92
		CA-A- 2096833	24-05-92
		EP-A- 0558623	08-09-93
		FI-A- 932331	21-05-93

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)